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Archives of Internal Medicine

VOLUME 53 JANUARY, 1934 NUMBER 1

CLINICAL AND PATHOLOGIC DIFFERENTIATION OF THE ACUTE LEUKEMIAS

WITH SPECIAL REFERENCE TO ACUTE MONOCYTIC LEUKEMIA

CLAUDE E. FORKNER, M.D.

PEIPING, CHINA

Friedreich [1] in 1857 reported a case of leukemia with an acute course. Ebstein [2] in 1889 described the clinical picture of acute leukemia. Fraenkel [3] in 1895 directed attention particularly to changes in the cells of the blood, and expressed the view that all acute leukemias were lymphogenous because of the similarity of the white blood cells of these patients to lymphocytes. Naegeli [4] in 1900 described the myeloblast, thereby permitting, on the basis of the cytologic characteristics, the separation of two types of acute leukemia, myeloblastic or acute myelogenous and lymphoblastic or acute lymphatic. A sharp differentiation, however, was not always clear owing to difficulties in technic of staining blood smears and because of atypical cases which defied classification.

Further elucidation of the problem was forthcoming in the discovery by Reschad and Shilling-Torgau [5] in 1913 of a third type of acute leukemia, acute monocytic leukemia. Although twenty years have elapsed since the appearance of this significant contribution, there have been only a few cases described. A recent review of the subject by Clough [6] mentioned only twenty-three cases which he considered to be adequately described and acceptable. These were recorded in the medical literature by twenty different groups of investigators. Of the twenty-

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, the Department of Medicine, Harvard University Medical School, and Peiping Union Medical College.

1. Friedreich, N.: Ein neuer Fall von Leukämie, Virchows Arch. f. path. Anat. **12**:37, 1857.

2. Ebstein, W.: Ueber die acute Leukämie und Pseudoleukämie, Deutsches Arch. f. klin. Med. **44**:343, 1889.

3. Fraenkel, A.: Ueber acute Leukämie, Deutsche med. Wchnschr. **21**:639, 663, 676, 699 and 712, 1895.

4. Naegeli, O.: Ueber rotes Knochenmark und Myeloblasten, Deutsche med. Wchnschr. **26**:287, 1900.

5. Reschad, H., and Schilling-Torgau, V.: Ueber eine neue Leukämie durch echte Uebergangsformen (Splenozytenleukämie) und ihre Bedeutung für die Selbständigkeit dieser Zellen, München. med. Wchnschr. **60**:1981, 1913.

6. Clough, P. W.: Monocytic Leukemia, Bull. Johns Hopkins Hosp. **51**:148, 1932.

three cases, all but six had been reported during the four years immediately preceding Clough's review, indicating that more and more cases were being recognized as the disease became better understood. During the past two years at the Thorndike Laboratory of the Boston City Hospital fifteen cases of acute leukemia in adults have been studied. Another case was studied in 1928. These sixteen cases have been equally divided between the three main types: myelogenous, lymphatic and monocytic. Postmortem examinations were made in four of the six cases of monocytic leukemia. One case of acute myelogenous leukemia and one of acute lymphatic leukemia with postmortem examinations of each are also recorded in this report as examples of the two other main types of acute leukemia.

The purpose of this report is to direct attention to certain clinical and pathologic features which appear to distinguish acute monocytic leukemia from the other forms of acute leukemia. The clinical and pathologic differences in this series of cases have been striking and of sufficient value to allow of a tentative diagnosis of acute monocytic leukemia independent of the studies on the blood. It seems reasonable to assume that a more general appreciation of the distinguishing features will result in the proper classification of many cases of acute monocytic leukemia which in the past have been unrecognized.

No attempt will be made to review the reported cases except to correlate certain features of these cases with those here reported. Adequate reviews of the disease have been published by Dameshek,[7] Clough,[6] and other physicians.

ACUTE MONOCYTIC LEUKEMIA

CASE 1.—*Medical History.*—W. C., a white man, aged 31, a professor, was admitted to the hospital complaining of soreness of the mouth and the throat.

His general health had always been good until about one and one-half years prior to admission, when he noticed that he became fatigued more easily than normal. This tendency had been more marked during the last few weeks before admission. He had had occasional occipital headaches for many years. He had always bruised rather easily. Scarlet fever and whooping cough occurred in childhood, but he had no other acute or chronic diseases. The family history was of no significance except that his mother died of pulmonary tuberculosis twenty-eight years previously.

The important features about the patient's dietary habits were that during the past few years he had eaten irregularly, often missing some meals entirely, owing to the nature of his work. Also he had always been very fond of dairy products, such as butter, cream, eggs and milk. He ate much more butter than the other members of his family, and felt that it was an important part of his food.

It was difficult to determine with certainty the onset of the present illness. The patient had been feeling a little under par for about eighteen months. Three

7. Dameshek, William: Acute Monocytic (Histiocytic) Leukemia, Arch. Int. Med. **46**:718 (Oct.) 1930.

months before admission he acquired a superficial infection of two fingers which did not clear up as quickly as such infections usually do. One month before admission he contracted a cold with an irritating, but nonproductive, cough which gradually got better over a period of three weeks, but never completely disappeared. His appetite was good until the onset of the cold and then gradually became poorer.

Two weeks before admission the lower front teeth became loose and the gums painful. This was associated with painful swellings in the left side of the neck and with a sore throat. Three days before admission ulcers appeared in the region of the swollen gums. These presenting symptoms brought him to the hospital.

Examination.—The patient was a well developed and well nourished man with moderate pallor and with marked swelling of the left side of the face extending over the maxillary and mandibular areas. The skin showed a few scattered petechiae over the trunk and a fine powdering of small petechiae over the lower part of the legs. On the back of his left forearm was a hemorrhagic area in the center of which there was a blister 1 cm. in diameter which was not tender. A few subcutaneous, blue, hemorrhagic areas, presumably bruises, were found over the extremities. The eyes were normal except for slight retinal edema and a few scattered hemorrhagic areas with yellowish-white centers in the retina.

The breath was very offensive. The gums were swollen and red. In some places they showed a purple discoloration and were soft. Ulceration was present about the margins of the gums, especially in the region of the upper molar and premolar teeth. Many of the teeth were loose. The tonsils were enlarged and reddened. Spirochetes and fusiform bacilli were present in the smears from the gums and tonsils. On the left side of the hard and soft palate there was an extensive submucous hemorrhage. The swelling of the left side of the face apparently was dependent on an extension of the infection from the mouth, presenting a picture of diffuse cellulitis.

The lymph nodes were generally moderately enlarged and slightly tender in the inguinal, axillary and cervical regions. Those in the cervical region measured from 1 to 2 cm. in diameter. A left epitrochlear lymph node was palpable.

The lungs were clear. The heart was within normal limits of size on percussion. The pulse rate was 110 per minute; the rhythm was regular. The blood pressure was 112 systolic and 60 diastolic.

The edge of the liver was palpable at the costal margin in the midclavicular line, and on percussion dulness in this line extended to the sixth rib. The edge of the spleen on full inspiration was felt 4 cm. below the costal margin. The abdominal muscles were somewhat rigid, and there was slight tenderness in the region of the spleen.

Neurologic examination revealed no abnormalities.

Laboratory Examinations.—Urinalysis showed: specific gravity, 1.015; sugar, none; albumin, a trace. The sediment contained numerous epithelial casts and a few leukocytes.

The Wassermann reaction of the blood serum was doubtful.

The nonprotein nitrogen of the blood was 76 mg. per hundred cubic centimeters. The coagulation time of the blood was twelve minutes by the method of Lee and White. The bleeding time was twenty minutes plus. The icteric index was 5 units. The blood cell count is shown in table 1.

TABLE 1.—*Studies on the Blood Cells in Acute Leukemia*

Case and Diagnosis	Date	Red Blood Cells, Millions per C.Mm.	Hemoglobin		White Blood Cells, per C.Mm.	Blood Platelets, Estimated or per C.Mm.	Nucleated Red Blood Cells per 100 White Blood Cells	Differential Leukocyte Formula								Comment
			Per Cent	Gm. per 100 Cc. Blood				Polymorphonuclear			Myelocytes of Various Types, per Cent	Myeloblasts, per Cent	Monocytes of All Ages, per Cent	Lymphocytes, per Cent	Unclassified, per Cent	
								Neutrophils, per Cent	Basophils, per Cent	Eosinophils, per Cent						
1 Acute monocytic leukemia	2/12/31	2.19	46	7.18	62,000	Marked decrease	...	0.5	0.5	...	0.5	....	94.0	4.5	...	94 per cent of cells contained fine oxidase granules
	2/13/31	2.28	47	7.33	92,500	Marked decrease	...	...	...	...	...	....	....	...	...	
	2/14/31	2.17	45	7.02	103,500	Marked decrease	...	2.5	...	3.0	1.5	....	87.5	5.0	0.5	
	2/16/31	1.75	39	6.08	72,500	Marked decrease	0.5	1.5	0.5	0.5	0.5	....	91.0	6.0	...	
	2/17/31	1.47	38	5.93	34,000	Marked decrease	...	1.0	...	...	1.0	....	94.5	3.0	0.5	
	2/18/31	1.69	32	4.99	124,500	Marked decrease	...	...	...	...	...	....	....	...	...	
	2/19/31	2.30	42	6.55	87,000	Marked decrease	...	...	...	...	...	....	....	...	...	
	2/20/31	2.02	39	6.08	103,000	Marked decrease	...	...	...	1.0	0.5	....	96.5	2.0	...	
	2/21/31	2.19	37	5.77	114,500	Marked decrease	...	...	...	0.5	1.5	....	96.0	2.0	...	
	2/22/31	1.90	41	6.40	77,500	Marked decrease	...	...	...	...	...	....	....	...	...	
	2/23/31	1.92	36	5.62	78,000	Marked decrease	...	...	...	...	...	....	....	...	...	
	2/24/31	1.97	35	5.46	87,000	Marked decrease	0.5	...	0.5	1.0	1.5	....	93.0	2.5	1.5	
	2/27/31	1.96	40	6.24	97,000	Marked decrease	...	2.0	...	2.5	...	....	93.0	2.0	0.5	
	3/ 2/31	1.59	33	5.15	150,500	Marked decrease	...	...	1.5	...	...	....	95.5	2.5	0.5	
2 Acute monocytic leukemia	4/ 8/31	3.00	72	11.23	74,000	Marked decrease	...	...	...	...	...	....	....	....	...	About 0.5 per cent of monocytes oxidase-positive
	4/ 9/31	....	..	.....	19,500	Marked decrease	...	3.5	...	0.5	2.5	....	71.5	21.0	...	
	4/10/31	3.24	77	12.01	33,500	Marked decrease	0.5	2.0	...	...	...	....	81.0	17.0	...	
	4/13/31	3.54	79	12.32	60,500	Marked decrease	...	...	...	...	...	....	....	....	...	
	4/15/31	3.65	80	12.48	82,500	Marked decrease	...	1.5	...	...	...	....	89.0	9.5	...	
	4/17/31	2.56	62	9.67	172,000	Marked decrease	...	0.5	...	...	0.5	....	95.0	4.0	...	
	4/17/31	....	..	....	166,330	Marked decrease	...	0.5	...	...	...	....	92.0	7.5	...	
	4/18/31	2.85	51	7.96	364,000	118,000	...	0.5	...	...	...	....	95.5	4.0	...	

Course.—The patient remained in the hospital for the last sixteen days of his life. No therapeutic measures that were tried were of any avail. Solution of potassium arsenite given by mouth seemed to be of no clinical value, although under such treatment the leukocytes decreased appreciably in number, but this effect was very transient. Three moderate doses of neoarsphenamine were given intravenously on Feb. 12, 16 and 24, 1931, but no improvement was apparent. Three transfusions of blood, each of 600 cc. of citrated blood given on February 19, 21 and 24, probably prolonged the patient's life for a few days. The local lesions of the mouth were treated with sodium perborate paste and solution and other cleansing washes which seemed to be of slight value. During the acute illness the temperature ranged from 100 to 103.5 F., and the pulse rate varied from 95 to 120 per minute. During the last few days of life bronchopneumonia of the middle lobe of the right lung, marked anemia, jaundice and signs of acute nephritis developed.

Postmortem Examination.—Gross Appearance: Petechial hemorrhages were present in the sclerae. The skin was markedly jaundiced. The mucous membranes of the buccal cavity, particularly those of the gums, were ulcerated, swollen and hemorrhagic. There was a generalized, discrete, pea-sized enlargement of the lymph nodes. One node in the left axilla measured 2.5 cm. in diameter. In the skin of the trunk and the extremities there were numerous small ecchymotic areas from 1 to 2 cm. in diameter. Over the insertion of the deltoid muscle in the right arm there was a hematoma 2 cm. in diameter with ecchymosis surrounding it for 3 cm. on all sides. There were numerous petechiae in the skin of the forearms and hands.

In the peritoneal cavity, the surfaces of the serosa, both parietal and visceral, were deeply jaundiced and full of petechial hemorrhages. All the adjacent surfaces throughout the cavity were adherent to each other by thin, filmy, yellowish strands simulating a very slight fibrinous exudate. These presented only slight resistance to separation of the surfaces affected. The domes of the diaphragm rose to the fourth interspace bilaterally. The edge of the liver was 9 cm. below the xiphoid process and 7 cm. below the costal margin in the midclavicular line. The spleen was much enlarged, and its lower pole was enveloped in the omentum. There were a few pea-sized, soft, grayish lymph nodes about the head of the pancreas and in the gastrohepatic ligament, but no palpable nodes in the mesentery.

There were petechiae and slight filmy adhesions in the pleural cavities.

The heart weighed 360 Gm. The myocardium was rather pale red and of normal consistence throughout; there was moderate hypertrophy of the left ventricle. There was slight fibrous thickening of the contact borders of the mitral valve.

The lungs were edematous and congested throughout. The lateral half of the right middle lobe was completely consolidated, quite firm and a grayish green, with a thick purulent exudate in the bronchioles. The hilar lymph nodes were slightly enlarged, soft and gray.

The spleen weighed 1,065 Gm. The capsule was thin and tense and varied in color from dark purple to red, in irregular blotches suggestive of capsular hemorrhages. The pulp was very soft and friable and dark brick red, with prominent trabeculae. The cut surface bulged on section and scraped away easily on the blade of the knife. There were several irregular lobulations around the hilus and lower pole that suggested accessory lobes.

The contents of the gastro-intestinal tract were dark greenish or a tarry color. There were multiple petechial hemorrhages throughout the mucosa from the

stomach to the end of the colon, but there was no evidence of frank hemorrhage from any single bleeding point. Bile flowed freely from the duodenal papilla.

The pancreas was very firm and hard throughout, but otherwise was normal.

The liver weighed 2,685 Gm. The surface was symmetrical, enlarged, smooth and gray. On section the liver was rather pale and firm in consistence, with prominent, slightly yellow, lobular markings, but there was no evidence of increased fibrous tissue. The gallbladder and bile ducts were normal.

The kidneys weighed 550 Gm. The fatty capsule was of a curious leathery consistence. The true capsule stripped readily, exposing a smooth pink surface. The renal tissue was soft and friable and on section appeared somewhat yellow. The cortex averaged fully 1.2 cm. in thickness; the pyramids were injected. The renal substance bulged on section. The calices contained a few small bits of orange gravel-like material and small blood clots. Otherwise, the pelves and the ureters were normal.

The suprarenal glands appeared to be normal.

The mucosa of the bladder was full of petechiae; otherwise the bladder was normal.

The genital organs were normal.

The aorta was slightly yellow, with soft atheromas.

The bone marrow was grayish pink and hyperplastic throughout.

The anatomic diagnosis was: leukemia; bronchopneumonia; acute pharyngitis; possibly acute nephritis; polyserositis (possibly fibrinous).

Microscopic Appearance: In the heart there were a few areas of focal infiltration of fat tissue with cells resembling monocytes, frequently showing mitoses.

There was marked edema of the lungs, with hemorrhages into the alveoli. Many alveoli were filled with monocytes, unclassifiable mononuclear cells and polymorphonuclear neutrophils in a network of fibrin. The alveolar walls were thickened by infiltration, with similar collections of cells. Many monocytes were filled with pigmented material.

The pulp of the spleen was densely infiltrated with large mononuclear cells, some with plentiful acidophilic, finely granular cytoplasm and large vesicular nuclei, others with a smaller amount of acidophilic cytoplasm and irregular vesicular nuclei. There were numerous mitoses in these cells; a few appeared to be multinucleated. Some of the larger cells appeared to have been phagocytic and contained granules, vacuoles, pigment and apparently red cells in the cytoplasm. The normal structure of the spleen appeared to be almost entirely obliterated.

There were foci of dense infiltration in the periportal tissue and in aberrant areas of the hepatic substance, with fibrin and cells similar to those described in the spleen except that large phagocytic monocytes were not present.

The stroma of the pancreas was everywhere densely infiltrated with the type cells.

The interstitial tissues of the kidneys, especially in the pyramids, were densely infiltrated with the cells described. No macrophages were present.

The perisuprarenal fat and fibrous tissue were densely infiltrated with monocytes and younger cells, as described in the spleen.

The structure of the lymph nodes was almost obliterated by dense infiltration with monocytes and younger forms.

The predominant cell in the bone marrow was a mononuclear cell with slight acidophilic cytoplasm and a fairly clear, vesicular nucleus. Many of the cells showed U-shaped nuclei. The macrophages were numerous and contained golden brown pigment and clear vacuoles. The majority of the cells were undoubtedly

monocytes. The formation of red cells was depressed. There seemed also to be a definite decrease in cells of the granulocytic series.

The microscopic diagnosis was monocytic leukemia.

CASE 2.—*Medical History.*—H. C., a white man, aged 38, married, a salesman, entered the hospital complaining of a sore mouth and weakness.

He was perfectly well until one month before admission, when he first noticed that his gums seemed more tender than usual and that they bled after brushing the teeth. He also noticed that he felt unusually tired after ordinary activities. A dentist was consulted; he made a diagnosis of "trench mouth" and gave the patient a mouth wash containing phenol, under which treatment the symptoms grew more intense. Smears from the gums were said to have been negative for pathogenic organisms. The patient was then seen by his physician; he found that the patient had slight anemia and gingivitis. Rest in bed and a diet consisting of liver and green vegetables were prescribed. Under this treatment his condition became worse, the gums became greatly swollen, he was feverish, and the weakness increased.

Two weeks before admission the patient had a dull ache across the sacrum and at the back of the head. This pain was transient, lasting a few hours, but recurred several times during the two weeks before admission.

Until one week before admission he worked steadily, driving an automobile about 200 miles a day. Two days before entering the hospital another physician was consulted; he found Vincent's organisms in the mouth and discovered that the patient had a high leukocyte count with many immature cells in the blood.

The past history was irrelevant. The patient had always been healthy and strong except for scarlet fever, chickenpox, measles and whooping cough in childhood.

The family history was of no importance except that one brother with whom the patient had been associated many years before had died of pulmonary tuberculosis.

The dietary history was of interest in that the patient had always eaten generously of fat, particularly cream and butter. His work as a traveling salesman had resulted in irregularity of meals, and frequently his food had been of poor quality. He was fond of vegetables and of meat and usually ate red meat and fresh vegetables at least once each day. He ate very little pastry or sweet foods. He smoked ten or twelve cigars a day and exercised very little.

Examination.—The patient was a well developed and well nourished man lying comfortably in bed without apparent discomfort. The skin, eyes, nose and ears were normal. The mucous membranes were slightly pale. The breath was very foul. The gums showed marked reddening and were greatly swollen or hypertrophied in some places, almost obscuring the sides of the teeth. At the back of the left central incissor tooth in the upper jaw was an area of necrosis, smears from which showed numerous fusiform bacilli and spirochetes. The tonsils were large, red and ragged. The pharynx was generally reddened. The tonsillar and submental lymph nodes were enlarged, measuring about 2 cm. in diameter. They were discrete and of moderately firm consistence, but not tender. The lymph nodes along the anterior borders of the sternocleidomastoid muscles, in the supraclavicular fossae and in the axilla, were similarly enlarged. A right epitrochlear lymph node was barely palpable. No lymph nodes could be felt in the pelvis, and those in the inguinal and femoral regions appeared to be normal.

The heart was slightly enlarged. The sounds were of good quality; the rhythm was regular, the rate being 86 beats per minute. There was a short soft systolic

murmur over the whole precordium. The blood pressure was 140 systolic and 64 diastolic. The lungs were normal to physical examination.

The spleen could be felt just below the costal margin, and was not tender. The edge of the liver extended 6 cm. below the costal margin in the midclavicular line. No other abnormalities were found.

Rectal examination revealed a tight sphincter and what appeared to be a small thrombosed external hemorrhoid which was moderately tender.

Examination of the genitalia, extremities and central nervous system revealed no abnormalities.

Laboratory Examinations.—The blood cell count and hemoglobin values are given in table 1.

The urine was yellow and acid, with a specific gravity of 1.012. There was no sugar, acetone or diacetic acid, but a slight trace of albumin. The sediment contained occasional hyaline and fine granular casts.

The nonprotein nitrogen of the blood was 28 mg. per hundred cubic centimeters. The icteric index of the blood serum was 10.6 units. A blood culture showed no growth. The bleeding time was four and one-half minutes. The coagulation time was twenty-four and one-half minutes (method of Lee and White).

The basal metabolic rate was +46 per cent.

Course.—Soon after admission solution of potassium arsenite was given by mouth for nine days, beginning with doses of 5 minims (0.3 cc.) three times a day and increased to 8 minims (0.5 cc.) three times a day. The number of leukocytes decreased, but the general condition of the patient grew worse, so that this medication was discontinued. Six days after admission the patient complained of severe pain in the rectum associated with defecation. Examination revealed swollen mucous membranes with a few nodular areas just within the anal sphincter. The rectum was dilated and one of the nodules excised for microscopic examination. The report of the pathologist was as follows: "A small nodule from the rectum showing infiltration with medium-sized cells with fairly numerous mitotic figures. The specimen is consistent with leukemic infiltration."

The necrosis of the gums increased, the anemia progressed, and the number of immature leukocytes in the blood became greater. The temperature, which on admission varied from normal to 100 F., increased to 102.5 F. Several days before death numerous petechiae appeared over the trunk and extremities and in the mucous membranes of the mouth and eyes. In spite of supportive treatment, the patient became weaker, râles developed in the bases of both lungs, and he died ten days after admission.

Postmortem Examination.—Gross Appearance: There was slight swelling of the lymph nodes in the left axilla to external palpation, but the others were not enlarged. There was no pitting edema. Scattered over the abdomen, especially in the left flank, were several bluish purpuric spots. At the left corner of the upper lip was a red-stained abrasion.

There was no free fluid in the peritoneal cavity. The peritoneal surfaces were smooth, glistening and without exudate. There were numerous subserous purpuric spots scattered over the visceral and parietal peritoneum. On the right, the diaphragm rose to the level of the third interspace, and on the left, to the fifth rib. The liver was 4 cm. below the xiphoid process and 4 cm. below the costal margin in the midclavicular line. The mesenteric lymph nodes were not enlarged.

There was a moderate amount of free, straw-colored, clear fluid in the left pleural cavity, but none in the right. A few easily broken adhesions bound both lungs to the posterior wall of the thorax. There was no fresh exudate.

There was a slightly increased amount of clear bloody fluid in the pericardial cavity, probably from a pericardial puncture performed shortly ante mortem. There were no adhesions.

The heart weighed 498 Gm. The myocardium was soft and of a grayish-red tinge, but showed no scarring. The valves showed no thickening or growths, and the endocardium was smooth. There were no antemortem clots. The coronary vessels everywhere were patent and without sclerosis.

The lungs were normal in size and shape and reddish gray. They were crepitant throughout without patches of consolidation. There was no pus. The vessels were patent. The hilar lymph nodes were slightly enlarged.

The spleen weighed 606 Gm. It was markedly enlarged, firm and gray-purple, with a smooth capsule. On section the pulp was a dark gray-red and appeared swollen; it tended to "round up" from the cut surface. No discrete follicles were observed. The surface scraped away rather easily.

The stomach and intestinal tract showed petechial hemorrhages throughout. The rugae of the stomach were not swollen. Peyer's patches of the ileum appeared to be normal. Masses could be felt in the rectal mucosa.

The pancreas was normal.

The liver weighed 2,670 Gm. It was markedly enlarged, brownish yellow, smooth on the surface and firm, with a rounded lower edge. On section the cut surface was yellow-brown, with dark brown mottling of the nutmeg type. The surface tissue was firm in consistence and could not be scraped away. The gall-bladder was normal.

The kidneys weighed 340 Gm. The capsule stripped with ease and revealed a grayish-purple, mottled, smooth surface. The cortex and medulla were slightly injected. The cortex showed no scarring or reduction in size, measuring on the average 7 mm. in thickness. There were no other abnormalities.

The suprarenal glands were normal.

The bladder was distended with clear, dark amber urine; otherwise, it was normal.

The penis was partially erected.

The aorta was normal.

Bone marrow taken from the fourth left vertebra was red and of normal consistence. Several ribs that were removed failed to show gross evidence of the areas of softening which had been recorded on roentgen examination. A small piece of bone from the greater trochanter of the left femur showed slight yellowish softening. Marrow from the cavity of the left femur was yellow and fairly firm.

The axillary nodes were enlarged, 3 by 2 by 2 cm., soft and gray-red. The lymph nodes at the bifurcation of the aorta and along the iliac arteries were moderately enlarged, soft and a grayish purple.

There were marked swelling and areas of necrosis in the gums.

The anatomic diagnosis was: generalized enlargement of the spleen, liver and lymph nodes; multiple petechial hemorrhages; hydrothorax, left; pulmonary edema and congestion; old pleuritis; gingivitis.

Microscopic Appearance: There was diffuse cellular infiltration of the muscle of the heart with cells, for the most part from 10 to 12 microns in diameter, with round, slightly indented, fairly deeply staining nuclei with a fine chromatin network and with thin circular veins of even neutrophilic cytoplasm. Most of the cells contained irregular, lobulated nuclei. There were occasional mast cells. The

vessels were filled with infiltrating cells. There was slight Zenker's degeneration of the muscle of the heart.

There was infiltration of the capillaries of the lungs with type cells. The alveoli were partially filled with serum, type cells, red blood cells and occasional fibrin precipitate.

In the spleen there was diffuse infiltration with type cells, both within the vessels and in the pulp. There were focal areas of necrosis. One multinucleated giant cell was seen. There were no typical megakaryocytes. Fibrin was present throughout.

The liver was infiltrated with type cells, especially in the periportal areas. There was fatty degeneration of the cells in the central zones, with necrosis of a few cells in the same regions. There were occasional cells that resembled nucleated erythrocytes. The oxidase reaction of the infiltrating cells was negative.

The kidneys showed infiltration of the glomerular tufts and the subcapsular, periglomerular and intertubular areas by type cells. There was slight tubular dilatation.

There were type cells in the vessels and perivascular spaces of the pancreas, with a few cells infiltrating the pancreatic substance.

The suprarenal glands showed diffuse infiltration by type cells. There was slight lumen formation.

The aorta showed infiltration of the adventitia and media by type cells.

The testes showed infiltration of the stroma by type cells.

The vessels of the submucosa of the stomach were filled with type cells. The tunica propria beneath the glands was infiltrated with type cells.

The lymph nodes had lost their normal structure. There was diffuse infiltration with type cells. There was an occasional cell resembling a nucleated red corpuscle. The adjacent blood vessels were filled with type cells. Monocytes phagocytosing lymphocytes and type cells were seen. There were no megakaryocytes.

The femoral bone marrow showed diffuse infiltration by type cells. Focal areas, which stained red, consisted of many red blood cells, and there was a more eosinophilic staining of the type cells themselves. There were many nucleated red blood cells which showed fragmentation of the nuclei.

In the bone marrow from the greater trochanter there were bits of bone without nuclei which took a heavy basophilic stain. There were a few type cells in the marrow.

The vertebral bone marrow showed diffuse infiltration of the marrow cavity by type cells, the nuclei of which stained more deeply and the cytoplasm of which was more bluish than elsewhere.

The microscopic diagnosis was monocytic leukemia.

Postmortem Culture.—A culture of blood from the heart showed no growth.

CASE 3.—*Medical History.*—S. W., a man, aged 40, single, a Polish laborer, entered the hospital on Oct. 23, 1931, complaining of headache, toothache and bleeding from the mouth.

The patient was perfectly well until about six weeks before admission, when it was noticed that his gums began to bleed slightly after brushing the teeth and after chewing hard foods. Also at this time it was noticed that the slightest injury caused the appearance of black and blue spots in his skin. These signs were not accompanied by any general discomfort, but gradually increased in intensity. The gums became swollen and tender.

Five days prior to admission severe aching in the region of the second left upper molar tooth occurred, accompaned by a generalized, dull, persistent headache. Two days before admission the patient consulted a dentist; he extracted the tooth. Extensive bleeding persisted for twelve hours in spite of packing. The patient estimated that about 2 quarts of blood had been lost. During the night there was slight continued oozing of blood. The next morning, one day before admission, he felt very weak and was unable to get out of bed. The aching subsided but the gums remained very tender.

The past history and family history were not significant. Nine years before admission an operation was performed for hemorrhoids. One year prior to the present illness the patient had been successfully treated for gonorrheal urethritis. He remembered no other illnesses. During the past six years he had severe constipation and had taken two compound cathartic pills practically daily. Without such medication his bowels would not move, and this condition was associated with frequent headaches.

The dietary history was important in that the patient ate very irregularly, and the quality of the food was usually poor. Rarely did he have fresh vegetables or fruit, except tomatoes, which he ate in large quantities. He drank moderately of poor quality alcohol or whisky about twice a week.

He had lost about 20 pounds (9 Kg.) during the last two years.

Examination.—The patient was a well developed and well nourished middle-aged man who looked pale, worn and apprehensive. There were obvious moderate swelling and redness of the whole left side of the face, more marked in the infra-orbital region. This area was moderately tender but not fluctuant. There were numerous small petechiae over both inguinal regions, the chest and the back. Several ecchymoses were present, from 2 to 3 cm. in size and irregular in contour, over the upper part of the right arm and the lower part of the left leg.

Except for some swelling of the lower lid of the left eye, the eyes were normal to routine physical and ophthalmoscopic examinations. The ears and nose were normal.

The breath was very foul. There was a large ulcerated area in the gums of the left side of the upper jaw, at the site of the extraction of the tooth. The margins of the ulcer, the buccal mucous membrane and the soft palate were hemorrhagic. Spirochetes and fusiform bacilli were present in a smear from the ulcerated area. There were several hemorrhagic vesicles on the lips on the left side. The teeth were dirty, but showed no obvious caries. The gums were generally hypertrophied and spongy. The tonsils were hypertrophied, but showed no evidence of acute infection except diffuse redness, which was present throughout the pharynx. The lymph nodes in the neck and right epitrochlear region were slightly enlarged. One lymph node, 1.5 cm. in diameter, in the left submaxillary region was tender, firm and freely movable.

The heart and lungs were normal on physical examination. The pulse rate was regular and of good quality. The blood pressure was 118 systolic and 70 diastolic. The spleen and liver were not palpable. There were no masses, spasm or tenderness in the abdomen. Examination of the bones and neuromuscular systems revealed no abnormalities except for absence of the abdominal reflexes.

Laboratory Examinations.—The results of studies on the blood are shown in table 2. The bleeding time was twenty-four minutes; the coagulation time, four minutes. The blood belonged to group IV (Moss classification). The Wassermann reaction of the blood was positive. A blood culture was negative in aerobic and anaerobic mediums.

TABLE 2.—*Studies on the Blood Cells in Acute Leukemia*

Case and Diagnosis	Date	Red Blood Cells, Millions per C.Mm.	Hemoglobin		White Blood Cells, per C.Mm.	Blood Platelets, Estimated or per C.Mm.	Nucleated Red Blood Cells per 100 White Blood Cells	Differential Leukocyte Formula								Comment
			Per Cent	Gm. per 100 Cc. Blood				Polymorphonuclear			Myelocytes of Various Types, per Cent	Myeloblasts, per Cent	Monocytes of All Ages, per Cent	Lymphocytes, per Cent	Unclassified, per Cent	
								Neutrophils, per Cent	Basophils, per Cent	Eosinophils, per Cent						
3 Acute monocytic leukemia	10/22/31	4.00	80	12.48	83,500	Marked decrease	...	...	...	...	...	...	....	...	...	Almost all cells oxidase-positive
	10/23/31	3.70	80	12.48	82,500	Marked decrease	0.5	2.0	...	...	...	....	96.0	1.0	1.0	
	10/26/31	3.84	78	12.17	72,000	Marked decrease	...	5.0	...	...	...	....	92.0	3.0	...	
	10/29/31	3.65	74	11.54	82,250	Marked decrease	0.5	2.5	...	0.5	...	....	96.5	0.5	...	
	10/31/31	3.34	70	10.92	87,000	Marked decrease	...	4.0	0.5	...	...	....	93.0	1.5	...	
	11/ 2/31	3.35	65	10.14	93,500	Marked decrease	0.5	3.0	1.0	...	...	....	95.0	1.0	...	
	11/ 5/31	3.38	66	10.30	95,000	Marked decrease	2.0	3.0	...	...	...	....	95.0	2.0	...	
	11/ 6/31	3.49	65	10.14	121,000	Marked decrease	1.0	6.0	3.0	...	...	...	90.0	1.0	...	
	11/ 7/31	3.52	64	9.98	119,500	Marked decrease	0.5	2.0	...	...	...	....	85.0	3.0	...	
	11/ 9/31	3.12	60	9.36	148,500	Marked decrease	...	9.0	2.0	...	...	....	86.0	2.0	1.0	
	11/10/31	3.06	56	8.74	169,500	Marked decrease	...	2.0	1.0	...	...	....	95.0	2.0	...	
	11/12/31	2.61	50	7.80	125,500	Marked decrease	1.0	3.0	...	...	...	....	96.0	1.0	...	
	11/13/31	2.46	50	7.80	73,000	Marked decrease	0.5	1.5	...	...	...	....	98.0	0.5	...	
	11/14/31	2.86	52	8.11	130,500	Marked decrease	1.0	2.0	...	...	...	....	97.0	1.0	...	
	11/16/31	2.56	50	7.80	140,500	Marked decrease	...	2.0	...	...	...	....	98.0	...	...	
	11/18/31	2.23	49	7.64	160,500	Marked decrease	5.0	4.0	...	...	...	....	95.0	1.0	...	
	11/19/31	2.42	50	7.80	242,000	Marked decrease	...	...	...	...	...	....	....	...	...	
	11/20/31	2.48	49	7.64	143,500	Marked decrease	4.0	5.0	...	...	...	....	93.0	2.0	...	
	11/21/31	2.14	..	....	122,000	Marked decrease	3.0	5.0	...	...	...	....	89.0	6.0	...	
	11/23/31	1.80	39	6.08	140,000	Marked decrease	3.0	2.0	...	...	2.0	....	95.0	1.0	...	
	11/24/31	1.90	39	6.08	169,500	Marked decrease	3.0	2.0	...	...	1.0	....	96.0	1.0	...	
	11/27/31	1.72	40	6.24	234,000	Marked decrease	19.0	4.0	...	...	...	....	95.0	1.0	...	

The urine was yellow and acid, with a specific gravity of 1.015. It contained a trace of albumin. Tests for sugar, acetone and diacetic acid were negative. The sediment contained a few white blood cells and an occasional red blood cell.

Gastric analysis showed no free hydrochloric acid in the contents taken during fasting or in those taken after an alcohol meal. The combined acid was 14 units.

The stool contained no ova or parasites. The guaiac test was negative.

A roentgenogram of the chest showed normal pulmonary fields.

Course.—During the first few days after admission to the hospital, the patient's general condition greatly improved with rest in bed and local treatment of the ulcerated lesions. The swelling of the face subsided, the ulcer became smaller, and the temperature, pulse rate and respiratory rate were reduced to normal. In spite of this improvement, the red blood cell and hemoglobin values greatly decreased.

One week after admission there was further bleeding from the gums, which recurred at intervals. Two weeks after admission pain and swelling recurred in the left maxillary region, and there was edema of the pharynx. The fever increased to 101 F., and the pulse rate to 110 beats per minute. A blood culture was again negative. On November 7, solution of potassium arsenite was given by mouth, beginning with doses of 5 minims three times a day, gradually increasing until November 21, when the patient was taking 11 minims (0.68 cc.) three times a day. No significant change occurred in the number or character of the white blood cells. The anemia progressed, and the general condition grew worse. There was evidence of consolidation in the bases of both lungs; this observation was confirmed by roentgen examination. The patient died on November 28, five weeks after admission.

Postmortem Examination.—Gross Appearance: The body was that of a well developed, but only fairly well nourished, white man showing slight rigor mortis and slight dependent lividity. The condition of the pupils could not be made out because of the shrunken condition of the eyelids. Over the lateral aspect of both arms and over the cubital space there were bluish areas representing puncture marks. Over the body generally there were small red petechial areas. There was clotted blood in both nostrils and ears and in the mouth. The axillary, cervical and inguinal lymph nodes were somewhat enlarged.

There was no increase of fluid in the peritoneal cavity. The peritoneum, particularly that covering the intestine, was dull, granular and slightly reddened. Small strands of fibrin could be peeled from these areas. The edge of the liver extended 8 cm. below the xiphoid process and from 3 to 4 cm. below the right costal border at the midclavicular line. The diaphragmatic domes were on a level with the fourth rib on the right and the fourth interspace on the left.

Both pleural cavities contained about 400 cc. of pure blood, most of which was not coagulated.

The surfaces of the pericardial cavity were normal, but the cavity contained 150 cc. of blood-tinged fluid.

The heart weighed 380 Gm. It was slightly increased in size and very flabby. The epicardium was smooth and the myocardium, pale red; the endocardium and valves were normal.

The lungs were covered with clotted blood. The posterior portion of each had diminished crepitus. Section showed a reddened parenchyma, particularly in the dependent portions. There was congestion throughout. On pressure a rather thick blood-stained fluid exuded.

The spleen weighed 360 Gm. It was enlarged and very soft. Section showed a soft reddish parenchyma the markings of which were very indistinct. Scattered throughout were small gray foci. The pulp scraped off easily.

The small and large intestines were considerably discolored; the mucosa was normal.

The liver weighed 2,200 Gm. The surface was smooth and pale gray-yellow. Section showed a parenchyma which for the most part appeared rather homogeneous. There were a few irregular areas with a slightly pink tinge. The consistence was normal. Bile flowed freely from the ampulla of Vater.

The kidneys weighed 460 Gm. Both organs were large and pale gray. Section showed a pale gray parenchyma. The pyramids and cortex were distinct. In the pelvis of each kidney there was blood, most of which was clotted. The ureters were normal.

The suprarenal glands, pancreas, bladder, genital organs and aorta were normal.

The lymph nodes of the axillary and cervical regions and of the groin were moderately enlarged, the largest measuring 3 cm. in diameter. The nodes were soft and on section showed a gray, soft parenchyma.

The bone marrow taken from the femur was fatty; that taken from the sternum and vertebra was paler than normal.

The anatomic findings were consistent with leukemia and hemothorax; there was a question as to whether bronchopneumonia had been present.

Microscopic Appearance: The microscopic changes in this case were similar to those in the two previous cases in that there was rather marked infiltration of the viscera with type cells. The type cells in this case were not as typical of monocytes as in the previous cases. The character of the cells was similar except that the nuclei for the most part were oval or round instead of elongated, folded or otherwise irregular. This suggested the possibility of the cells being myeloblasts or early myelocytes rather than monocytes. However, study of the blood during life, by means of the supravital technic, convinced me that the abnormal cells belonged to the monocytic strain. The oxidase reaction of the abnormal cells in the tissues, as in the blood, was positive, but the granules were fewer and finer than those usually encountered in early myelocytes.

The bone marrow, lymph nodes and spleen, as in the previous cases, were hyperplastic, with almost complete obliteration of the normal architecture.

The microscopic diagnosis was acute leukemia, probably monocytic.

CASE 4.—*Medical History.*—E. L., a white man, aged 26, married, a telephone lineman, came to the hospital with the complaint of ulcerated, bleeding gums and general weakness.

An accurate history was unobtainable in that the patient was in a critical state on admission, from which he made no recovery.

About two weeks before admission the patient complained of severe toothache. A dentist was consulted; he extracted two upper incisor teeth. This was followed by profuse hemorrhage for several hours, which was finally checked by packing the bleeding cavities with gauze. Although the patient had felt quite well until the onset of the toothache, from this time on he became progressively weaker. Eight days after extraction he became acutely ill and had a high fever.

The past history could not be obtained in detail. It was learned that for the past two years, following an appendectomy, the patient had not felt as strong as previously, and had suffered from recurrent attacks of abdominal pain.

Examination.—The patient was a well developed and well nourished man in a semicomatose state, markedly dyspneic and cyanotic; he frequently spat up bright blood. He occasionally opened his eyes and answered simple questions.

The skin was moist and hot, but there were no petechiae, ecchymoses or other lesions of the skin. The mucous membranes were pale and cyanotic.

Examination of the ears, nose and eyes revealed no abnormalities. No hemorrhages or areas of leukemic infiltration were present in the fundus.

The breath was very foul; the gums were ulcerated and gangrenous. There was clotted blood over the teeth and gums. The lips were cyanotic. The teeth were in fair condition, except for two upper incisors, which had recently been extracted; the cavities were filled with clotted blood. There were a few petechiae in the mucous membranes of the hard and soft palate and of the cheeks. The tonsils were not enlarged.

In the neck the lymph nodes were moderately enlarged, from 0.5 to 2 cm. in diameter. The lymph nodes in the axillae and groins also were moderately enlarged. There was definite but slight dulness over the bases of both lungs, together with suppression of breath sounds. No râles or rubs were heard. The rate of respiration was 30 per minute. Aside from a soft systolic murmur at the apex and some accentuation of the aortic second sound, the heart was normal on examination. The spleen was felt 3.5 cm. below the costal margin. Its edge was rounded and only moderately firm. The liver extended 4 cm. below the costal margin in the midclavicular line and was not tender. No other masses or tenderness was found. Examination of the extremities and of the neuromuscular system revealed no abnormalities.

The history and physical findings in this case were so similar to those of the three previous cases that a tentative diagnosis of acute monocytic leukemia was made before the blood was actually examined.

Owing to the patient's critical condition on admission, he was given a transfusion of 600 cc. of citrated blood. There was no untoward reaction, and no improvement followed. Later in the same day bronchial breathing was heard over the upper portion of the lower lobe of the left lung. The patient died twenty-five hours after admission.

Laboratory Examinations.—The results of studies on the blood are shown in table 3. The nonprotein nitrogen of the blood was 40 mg. per hundred cubic centimeters; the blood sugar, 80 mg. The bleeding time was prolonged. The Wassermann reaction of the blood was negative. A blood culture showed pneumococcus, type 18.

The urine was yellow, acid and cloudy; the specific gravity was 1.010. It contained a trace of albumin, granular and hyaline casts and an occasional white blood cell; sugar was not present.

Postmortem Examination.—Gross Appearance: The body was that of a well developed and well nourished white man. There were very slight rigor mortis and slight dependent lividity. Edema was not present. There were tattoo marks on the right forearm, and the scar of a lower right rectus incision was seen in the abdominal wall. A few small firm lymph nodes about 1 cm. in diameter were palpable in both inguinal regions. The other superficial lymph nodes were not palpable.

The peritoneal cavity contained no free fluid. There were a few old fibrous adhesions about the abdominal wound in the cecal region. The appendix was absent. The mesenteric lymph nodes were moderately and uniformly enlarged: those at the root of the mesentery averaged about 1.5 cm. in diameter. They were soft, uniform and pinkish gray on the cut surfaces. The diaphragm extended to the fifth space on the right and to the sixth rib on the left.

TABLE 3.—*Studies on the Blood Cells in Acute Leukemia*

Case and Diagnosis	Date	Red Blood Cells, Millions per C.Mm.	Hemoglobin		White Blood Cells, per C.Mm.	Blood Platelets, Estimated or per C.Mm.	Nucleated Red Blood Cells per 100 White Blood Cells	Differential Leukocyte Formula								Comment
			Per Cent	Gm. per 100 Cc. Blood				Polymorphonuclear			Myelocytes of Various Types, per Cent	Myeloblasts, per Cent	Monocytes of All Ages, per Cent	Lymphocytes, per Cent	Unclassified, per Cent	
								Neutrophils, per Cent	Basophils, per Cent	Eosinophils, per Cent						
4. Acute monocytic leukemia	9/11/31	3.24	54	8.42	52,700	Very few	...	5.0	...	...	7.0	....	77.0	7.0	4.0	From 85 to 95 per cent of cells oxidase-positive
	9/12/31	4.16	54	8.42	73,500	Very few	3.0	9.0	...	...	8.0	....	81.0	2.0	...	
5 Acute monocytic leukemia	10/13/31	2.10	..	....	160,000	Very few	...	...	...	...	...	....	....	....	...	25 per cent of abnormal cells with many fine oxidase granules; 50 per cent of abnormal cells with few fine oxidase granules; 25 per cent of abnormal cells oxidase-negative
	10/15/31	1.60	36	5.62	128,000	Very few	...	8.0	...	...	...	....	75.0	17.0	...	
	10/19/31	1.81	33	5.15	110,500	Very few	...	2.0	...	...	1.0	....	94.0	3.0	...	
	10/23/31	....	..	....	74,200	Very few	...	...	...	...	...	....	....	....	...	
	10/31/31	0.90	15	2.34	104,000	Very few	...	25.0	...	...	...	....	67.0	8.0	...	
6 Acute monocytic leukemia	12/17/28	1.61	50	7.80	71,000	Marked decrease	...	8.0	...	...	6.0	....	70.0	16.0	...	No oxidase stains used
	12/18/28	1.65	..	....	73,750	Marked decrease	1.6	19.0	...	...	9.0	....	65.0	4.0	...	
	12/21/28	1.71	40	6.24	93,400	Marked decrease	...	7.0	...	...	1.0	....	79.0	13.0	...	
	12/22/28	2.00	45	7.02	99,800	Marked decrease	...	6.0	...	...	3.0	....	82.0	9.0	...	
	12/23/28	1.84	45	7.02	110,000	Marked decrease	...	2.0	...	...	1.0	....	88.0	10.0	...	
7. Acute myelogenous leukemia	1/14/31	0.83	20	3.12	121,000	Absent	0.5	1.5	...	...	3.5	92.0	0.5	2.0	0.5	27 per cent of cells contained a few large oxidase granules
	1/15/31	0.77	..	....	194,000	Absent	...	...	...	...	...	....	...	...	...	
8 Acute lymphatic leukemia (leukosarcoma)	1/28/31	3.07	51	7.96	1,110,000	Very few	...	1.5	...	...	0.5	....	...	98.0	...	All lymphocytes oxidase-negative
	1/29/31	2.74	53	8.27	920,000	Very few	...	...	...	...	...	....	...	....	...	
	1/30/31	3.01	53	8.27	795,000	Very few	0.5	0.75	...	...	0.5	....	...	98.75	...	

The pleural cavities contained no free fluid. The parietal pleura was not examined because of restriction.

The pericardial cavity and the heart were not examined because of restriction. The heart was not enlarged to palpation.

The lungs weighed 1,530 Gm. They were crepitant throughout save for an area about 5 cm. in diameter in the upper posterior part of the lower lobe of the left lung. On cut surface this area was poorly demarcated, grayish red and drier than the surrounding lung. In addition there were scattered patches of consolidation from 0.5 to 1 cm. in diameter throughout both lungs.

The spleen weighed 900 Gm. It was markedly enlarged. The cut surface was uniformly grayish red and rather dry.

The small lymph nodes close to the mesenteric attachment were uniformly moderately enlarged. Peyer's patches did not appear to be enlarged. The gastrointestinal tract was otherwise normal throughout.

The pancreas was normal.

The liver weighed 2,900 Gm. It was considerably enlarged, and extended 12 cm. below the xiphoid process and 8 cm. below the costal margin in the midclavicular line. The surface was smooth, and the lobulation was rather prominently visible through the capsule. The cut surface was paler than normal, with slightly accentuated markings. The consistence was normal.

The kidneys weighed 720 Gm. and were considerbly enlarged. The right pelvis and ureter were moderately dilated, but no anatomic cause could be discovered. The capsules stripped readily, leaving a smooth surface. The cut surface was pale, and the renal substance showed marked streaking and mottling with yellowish-white tissue.

The medulla of the suprarenal glands was liquefied. The cortex appeared normal.

The bladder was distended with about a liter of clear urine, but was otherwise normal.

The genitalia appeared to be normal.

The aorta was elastic and normal throughout.

The vertebral marrow was very hard, calcified and a uniform grayish pink.

The anatomic diagnosis was: bronchopneumonia; generalized lymphatic enlargement; splenomegaly; enlargement of the liver and kidneys; cellular infiltration of the bone marrow; hydronephrosis, right. The anatomic findings were consistent with leukemia.

Microscopic Appearance: No sections of the heart were taken.

The alveoli of the lungs throughout were filled with coagulated serum, leukocytes, occasional hemorrhage and irregular masses of fibrin, chiefly around the bronchi. The leukocytes were chiefly monocytes. In addition, there were many very large cells with single or multiple vesicular nuclei and cytoplasm filled with very finely granular brown pigment. The bronchioles were filled with plugs of fibrin and leukocytes, showing a predominance of mononuclears. The interalveolar capillaries were congested and contained large numbers of monocytes.

The lymphoid nodules of the spleen were crowded out, and the pulp spaces were distended by large numbers of mononuclear cells. Many of the larger mononuclears contained masses of brown pigment and partly digested red blood cells. Occasional megakaryocytes were present in the pulp. The endothelium of the larger arteries was lifted from the media by a considerable accumulation of monocytes.

The portal spaces of the liver contained many lymphocytes and mononuclear cells. The sinusoids were uniformly distended with large numbers of mononuclear cells. There were a few small areas of subintimal infiltration in the large veins.

The pancreas was normal save for large numbers of mononuclear cells in the vessels.

There was an occasional small accumulation of mononuclear cells in the stroma of the cortex and medulla of the kidneys. Moderate hydropic swelling of the epithelium of the convoluted tubules was noted. Like the vessels elsewhere, the glomerular capillaries contained many mononuclear cells.

There was very marked lipoid disintegration of the zona fasciculata of the suprarenal glands. There was a marked diffuse accumulation of lymphocytes and mononuclear cells in the stroma.

The structure of the lymph nodes was almost completely replaced by a diffuse infiltration with mononuclear cells, only partially limited by the capsule, and extending into the surrounding tissue. Megakaryocytes were present in all the nodes, but were extremely numerous in one section in which they had actually engulfed mononuclear cells. The oxidase test showed a large number of oxidase-positive cells.

The bone marrow was very hyperplastic. The red cell series was crowded out by masses of cells of the mononuclear type. Very few cells of the granular series were present; megakaryocytes were numerous. Occasional mitoses were present. The type cell was one of moderate size, with nongranular, fairly abundant neutrophilic cytoplasm and a single more or less indented vesicular nucleus, closely resembling the blood monocyte.

The microscopic diagnosis was monocytic leukemia with leukemic infiltration of the spleen, liver, kidneys, lymph nodes and suprarenal glands.

Postmortem Bacteriologic Studies.—A culture from the lungs showed Streptococcus viridans, Staphylococcus aureus and Pneumococcus, type 18. A culture from the liver showed Staphylococcus aureus and Streptococcus viridans.

Case 5.—*Medical History.*—A. C., a white high-school girl, aged 16 years, entered the hospital on Oct. 13, 1931, complaining of weakness, spots over the body, bleeding from the nose and soreness of the gums.

The patient had not been in good health for five months before admission, at which time she began to feel languid and did not care to take part in any activities, but preferred to remain quietly at home. The appetite became poor, and she complained of attacks of giddiness.

Three months before admission the patient noticed shortness of breath on moderate exertion. At this time her gums began to bleed after brushing the teeth, and she noticed for the first time discolored bluish spots under the skin sometimes occurring spontaneously but more frequently produced by slight trauma.

Two months prior to admission she had a sore throat. Examination by her physician revealed large tonsils, but owing to the tendency to bleed, operation was avoided. She frequently spat blood from her gums and from the posterior part of the pharynx. The tonsils remained enlarged and tender throughout the present illness.

Two weeks before admission blurring of vision occurred, and the patient had prolonged flowing of blood from the uterus, which persisted. The gums became more tender, the teeth loosened, and the breath was very offensive.

The family history was irrelevant. The past history revealed no illnesses except mumps and chickenpox early in childhood and a mild attack of pain in the joints,

probably rheumatic fever, four years prior to admission. The patient had always been extraordinarily well and strong until the present illness. Her dietary habits were good, and there were no idiosyncrasies or peculiarities in her diet. Her best weight was 154 pounds (69.9 Kg.), six months before admission. During the present illness she lost 13 pounds (5.9 Kg.).

Examination.—The patient was a young, tall, white, fairly well nourished and well developed American girl lying in bed in considerable discomfort with obvious lesions of the mouth.

The skin was pale, and many small petechial hemorrhages and larger ecchymoses were scattered over the neck, trunk and extremities. The mucous membranes were pale. Small hemorrhages were seen in the conjunctivae. The mucous membranes of the nose were injected, swollen and possibly hypertrophic. The epithelium of the lips and buccal cavity was swollen; the gums were spongy and hypertrophic. There were numerous hemorrhages into the mucous membranes of the mouth.

The pupils were equal and reacted normally to light and in accommodation. The retina was somewhat hyperemic, and several small hemorrhages were present in the right retina. The margins of the optic disks were somewhat indistinct.

The mouth was as described in the history, and the breath was very foul; several teeth were loose, and three teeth were badly decayed. There were several necrotic, gangrenous ulcers of the gums. The tonsils were considerably enlarged and injected.

The lungs were normal on physical examination, and roentgenograms revealed only moderate thickening of the roots of both lungs.

The heart was slightly enlarged to the left. A soft systolic murmur was present over the whole precordium, and a short diastolic murmur was heard at the apex. The blood pressure was 110 systolic and 64 diastolic.

The results of examination of the abdomen were not remarkable except that the liver and spleen were palpable about 2 cm. below the costal margins and were slightly tender.

Pelvic examination was not made because the patient was menstruating.

The neurologic findings were normal except for congestion of the optic nerve head.

The lymph nodes generally were slightly enlarged. Those in the cervical, left axilla and left inguinal regions were moderately enlarged, varying from 0.5 to 2 cm. in diameter.

Course.—The patient remained in the hospital eighteen days and grew progressively more ill. Numerous new ecchymoses appeared over the trunk, extremities and mucous membranes. Bleeding of the gums and frequent epistaxis occurred. Two transfusions of blood were given on October 20 and 23; they were of very transient benefit. The body temperature fluctuated between 98 and 103 F. The pulse rate varied from 120 to 160 beats per minute, and the respiratory rate, from 25 to 30 per minute. She became rapidly weaker and died on October 31. Permission for autopsy was denied.

Laboratory Examinations.—The results of studies on the blood are shown in table 3.

Urinalysis showed: specific gravity, 1.015; sugar, none; albumin, ++. The sediment contained several red blood corpuscles in each high power field. Occasional hyaline and granular casts were seen.

The stools were formed and dark. There was a strongly positive guaiac test for occult blood.

The sputum was negative for acid-fast bacilli. Numerous streptococci were present.

A smear from the ulcerated gums showed many fusiform bacilli and spirochetes.

The icteric index of the blood serum was 6 units. The bleeding time was much prolonged.

On admission roentgen examination of the chest revealed moderate thickening of the roots of both lungs, the pulmonary fields being otherwise clear.

CASE 6.—*Medical History.*—W. L., a white man, aged 32, married, a chauffeur, entered the hospital on Dec. 12, 1928. He stated that he was perfectly well until about ten weeks before admission, when it was noticed by his wife and friends that he was pale. His physician was consulted; he was given tonics and advised to stop work. No examination of the blood was made at this time.

Eight weeks before admission the patient noticed anorexia, and he felt tired. He stopped work but continued to feel distinctly under par. At this time he first noticed slight pain in the right side of the upper jaw which persisted and became more marked. The anorexia increased, and he occasionally vomited in the morning. He failed to sleep well and began to lose weight rapidly.

Two weeks before admission the patient complained to his physician of painful hemorrhoids which, however, did not bleed. On previous occasions during the past two years he had had some discomfort from mild bleeding hemorrhoids. Pallor was becoming more marked, and he was definitely short of breath on exertion.

One week before admission marked sweating occurred, and the patient experienced several chills. The pain in the right side of the upper jaw became more annoying, and three days before admission a dental bridge was removed. The gums became markedly swollen and tender. He had lost 15 pounds (6.8 Kg.) during the last few weeks.

The only disease which the patient remembered having was typhoid fever at the age of 10 years. He stated that he had always been irregular in his sleeping and eating habits. No other significant dietary history was obtained. During the past two years he had worked considerably with ethyl gasoline and noticed that the gasoline fumes frequently made him feel nauseated. The family history was of no significance, except that his mother had died many years before of tuberculosis.

Examination.—The patient was a pale, well developed and moderately well nourished young man lying in bed in obvious discomfort owing to swelling and soreness of the face on the right side.

The skin was sallow, and a few small, fresh hemorrhages were present over the trunk.

The mouth was the site of chief discomfort. The teeth were poorly kept and contained a few cavities. The gums were greatly swollen, and in the region of the right upper molars there was a large, tender, sloughing, ulcerated area. The swelling extended to the whole right side of the face and was of distinctly higher temperature than the other side. The mucous membranes of the pharynx were swollen and injected; the tonsils were moderately enlarged.

The heart was not enlarged, and no abnormal sounds were heard, but the rate was rapid, 110 per minute. The blood pressure was 120 systolic and 75 diastolic. The lungs were normal to percussion and auscultation.

The liver and spleen were palpable 1 cm. below the costal margin and were slightly tender.

There was moderate general enlargement of the lymph nodes.

The extremities were normal. Neurologic examination revealed no abnormal findings.

Course.—The anemia, which was severe on admission, became somewhat more intense. The lesions in the mouth progressed. The body temperature varied from 98.4 to 104 F. Blood cultures were positive for Staphylococcus albus, Streptococcus haemolyticus and Bacillus coli-communis. The pulse rate fluctuated between 110 and 120, and the respiratory rate, from 25 to 40 per minute. The patient gradually became more dyspneic and died on December 23, eleven days after admission. Permission for autopsy was not obtained.

Laboratory Examinations.—The results of studies on the blood are shown in table 3.

The urine was negative for sugar. Albumin was constantly present in moderate amounts. White blood cells and hyaline and granular casts were present in increased numbers in the sediment.

The blood sugar was 113 mg. per hundred cubic centimeters. The nonprotein nitrogen of the blood was 37 mg.

Cultures from the gangrenous gums showed Streptococcus haemolyticus.

Roentgenograms of the teeth showed no abscesses.

ACUTE MYELOGENOUS LEUKEMIA

CASE 7.—*Medical History.*—P. G., a white American youth, aged 17, entered the hospital with the complaint of bleeding from the mouth following extraction of a tooth.

The patient was in a critical condition and semicomatose on admission. No relatives or associates could give a detailed history. He was, so far as could be learned, perfectly well until one week before admission, at which time a tooth was extracted. There was profuse bleeding, said to be about a liter, at the time of extraction, and moderate bleeding continued throughout the week until admission. No information concerning the past history or family history could be obtained.

Examination.—The patient was a fairly well developed and fairly well nourished young man, semicomatose, moderately dyspneic and very pale. There were numerous very small petechial hemorrhages scattered over the trunk and extremities. The mucous membranes were very pale and were the sites of small hemorrhages. There was oozing of blood from a tooth cavity and around the edges of the remaining teeth, but there was no ulceration, gangrene or diffuse swelling of the mucous membranes. There were several rather extensive hemorrhages into the mucous membranes of the lips.

A complete physical examination was not done owing to the patient's critical state. The lymph nodes in the neck, axillae and inguinal regions were not enlarged. The heart was slightly enlarged, and there was a blowing systolic murmur over the whole precordium. The pulse rate was 120 per minute. The lungs were normal. The edge of the liver could not be felt, and the edge of the spleen was palpable only on deep inspiration. No other abnormalities were noted. On one examination the urine showed no sugar, a trace of albumin and no acetone or diacetic acid. The urinary sediment contained a few white blood cells, red blood cells and occasional hyaline and granular casts. The results of the study of the blood are shown in table 3.

Course.—Soon after admission to the hospital a transfusion of 400 cc. of citrated blood was given. The next day the patient was obviously in a more critical state. The body temperature was 102 F.; the pulse rate rose to 160 beats per minute, and the respiratory rate to 45 per minute; there was marked dyspnea. In spite of supportive treatment, the patient died about thirty-six hours after admission.

Postmortem Examination.—Gross Appearance: No lymph nodes were palpable except a few in the inguinal region, measuring 1 cm. in diameter. The skin and mouth were as described in the physical examination recorded. The peritoneal serosa was smooth and without exudate. The domes of the diaphragm rose to the fifth rib on the right and to the fifth interspace on the left.

The liver weighed 2,030 Gm., and its edge was 2 cm. below the right costal margin. Its capsule was thin and the surface smooth. Section of the liver showed a pale, grayish mottling on a light brown background. The consistence was soft. The gallbladder was normal.

The spleen weighed 240 Gm. The capsule was thin and smooth. A section through the organ revealed a soft purplish-gray surface with numerous round, gray areas from 2 to 3 cm. in diameter scattered throughout. The cut surface scraped away with ease.

The pancreas and suprarenal glands were normal.

The kidneys weighed 380 Gm. The capsules stripped with ease, leaving smooth surfaces. The cortex was uniform and measured 6 cm. in width. The renal tissue was pale and somewhat soft, but otherwise normal.

The gastro-intestinal tract, genital organs, abdominal vessels and urinary bladder were normal.

The surfaces of the pericardial cavity were smooth. About 75 cc. of clear amber-colored fluid was present.

The heart weighed 440 Gm. There were marked dilatation and slight hypertrophy. Beneath the visceral pericardium were numerous red areas from 1 to 2 cm. in diameter. The heart muscle was soft and pale and showed no areas of scarring. There were numerous small endocardial hemorrhages. The valves and the coronary vessels were normal.

The pleural cavities were normal.

Both lungs were soft and light in color. No areas of consolidation or of scarring were found.

Sections of the bone marrow were removed from the sternum, vertebrae and femur. The marrow was soft and grayish pink and appeared to be hyperplastic.

Microscopic Appearance: The blood vessels of the heart and lungs were filled with large white blood cells which contained large round nuclei with rather coarse chromatin masses. The cytoplasm of these cells was small or moderate in amount, blue staining and granular. Occasional cells were present with blue granules. No other abnormalities were noted in these organs.

The sinuses of the spleen were filled with cells. Many areas were present in which fibrin had been deposited, and hyaline changes had occurred. The architecture of the spleen was partially obliterated by the cellular hyperplasia.

There was extensive central necrosis of the liver, with some extravasation of red blood corpuscles. The sinusoids were distended and filled with cells similar to those described in the vessels of the heart and lungs. There was slight infiltration of the periportal connective tissue with these cells.

The pancreas was normal.

The renal tubules were distended. The blood vessels were the same as those in the heart.

The suprarenal glands showed slight infiltration with the type cells as described in the blood vessels.

The sinuses of the lymph nodes were filled with the type cells. The architecture was somewhat distorted.

In the bone marrow there was marked hyperplasia, the large uninuclear cells predominating. These cells appeared to be myeloblasts and early myelocytes. The areas of formation of red blood corpuscles were greatly reduced in number.

The microscopic diagnosis was myelogenous leukemia.

Postmortem Cultures.—Cultures of the heart's blood and bone marrow showed no growth.

ACUTE LYMPHATIC LEUKEMIA (LEUKOSARCOMA)

CASE 8.—*Medical History.*—C. T., a white American schoolboy, aged 10 years, entered the hospital on Jan. 28, 1931, because of cough, pain in the abdomen and pallor.

The past history was not remarkable except that two years before admission the patient had whooping cough, measles and chickenpox with uneventful recoveries. Aside from occasional colds he had no other illnesses. The family history was not significant. The patient had received an adequate diet, and there was no history of abnormalities in his likes or dislikes for special articles of food.

Six months before admission the school physician had reported disease of the tonsils and adenoids, but no operation or other treatment was advised or undertaken.

Six weeks before admission the present illness began with a persistent cough. The patient had no fever and was not kept in bed, but he did complain of some pain between the shoulders and in the upper part of his abdomen.

The family physician found no abnormalities. Soon afterward his mother noticed that the child was becoming pale, was breathless on moderate exertion and was taking less food than usual. He was given cough medicine, which brought about some improvement, but his appetite remained poor, and soon the cough became more troublesome.

Three weeks before admission a moderate nosebleed occurred. The family physician again examined the patient, but found nothing abnormal. No studies of the blood were made at this time.

One week before admission all the symptoms became more severe, and the patient's physician discovered an enlargement of the spleen. The left eye became discolored as the result of a spontaneous hemorrhage. The urine was found to be normal.

After a few days a consultant made a diagnosis of acute leukemia, and the patient was referred to the hospital.

He had no bleeding or ulceration and no pain in his mouth or pharynx.

Examination.—The patient was quite emaciated, sitting propped up in bed, with obvious discomfort. The skin was pale and contained only two moderate-sized petechial hemorrhages. There were large subconjunctival hemorrhages in each eye and what appeared to be a hemorrhage into the deeper structures behind the eyeball on the left side. Examination of the fundi showed numerous small hemorrhagic areas with grayish centers, the type of lesion so often seen in leukemia. There were a few crusts of blood in the nose but no discharge. The lips were slightly cyanotic. The mucous membranes of the mouth and pharynx were in good condition, except for a few small petechial hemorrhages on the soft palate. There was no ulceration or swelling of the gums. The tonsils were enlarged and cryptic, but presented no evidence of acute infection.

There was rather marked general enlargement of the lymph nodes. In the neck these nodes were firm and discrete, about 0.5 cm. in diameter. In each axilla there were masses of lymph nodes some of which were from 2 to 5 cm. in diameter.

firm, smooth and not tender. Both epitrochlear lymph nodes were easily palpable and were about 1 cm. in diameter. There were enlarged inguinal nodes, and a mass of lymph nodes could be felt in the pelvis just under the pubic ramis.

The chest was rather asymmetrical, with a large anteroposterior diameter and some fulness in the upper part of the left side. The percussion dulness over the anterior mediastinum was of interest. In the second interspace the substernal dulness was 9 cm. in width. The left border of cardiac dulness was 11.5 cm. to the left of the midsternal line in the sixth intercostal space. No murmurs were heard. The pulse was regular, rapid (130 per minute) and of low volume. The blood pressure was 90 systolic and 60 diastolic. The pulmonary fields showed slight impairment of the percussion note over the upper lobes on each side, and in this area there was high-pitched tubular breathing together with accentuated whispered breath sounds. There were a few moist râles in the bases of both lungs.

The abdomen was full. The edge of the liver was smooth and slightly tender 7 cm. below the right costal margin in the nipple line. The spleen extended 12.5 cm. below the costal margin in the nipple line.

Examination of other parts of the body showed them to be normal, except that the deep reflexes of the extremities were not obtained, possibly because of the semicomatose condition of the patient.

Laboratory Examinations.—The blood was remarkable (table 3). There were 1,110,000 white blood cells per cubic millimeter, one of the highest white blood cell counts on record. The Wassermann reaction of the blood was negative.

The urine was yellow and neutral to litmus; it contained no sugar, acetone or diacetic acid; the specific gravity was 1.025. There was a trace of albumin. The sediment contained a few red and white blood cells.

Course.—Soon after admission to the hospital the patient was given a transfusion intravenously of 300 cc. of normal citrated blood. He was also given intravenously, purely as a trial, two small doses of pentnucleotide. The body temperature varied from normal to 100.8 F., and the pulse rate and respiratory rate were constantly elevated from 125 to 140 per minute and from 32 to 55 per minute, respectively. The patient lapsed further into coma and died three days after admission.

Postmortem Examination.—Gross Appearance: The external appearance was as described in the clinical history.

The surfaces of the peritoneal cavity were smooth. The domes of the diaphragm rose to the sixth rib on the right side and to the seventh rib on the left. The edge of the liver extended 11.5 cm. below the xiphoid process and 10 cm. below the right costal margin in the midclavicular line. The appendix was normal. The mesenteric lymph nodes were enlarged, from 0.5 to 1.5 cm. in diameter, and were firm in consistence.

The right pleural cavity contained about 1,000 cc. of amber-colored fluid. The anterior mediastinum was obliterated by a tumor extending from the sternal notch to the xiphoid process. This mass was adherent to the sternum for a distance of 3 cm. on either side of the midline. The posterior limits of the mass were the pericardium, which it completely covered. The tumor tissue had invaded the medial surfaces of both lungs, particularly on the right side. The middle and lower lobes of the right lung were collapsed and almost completely invaded by tumor tissue. This tissue was hard and yellowish white. The thymus gland could not be identified, but presumably was completely destroyed by the tumor.

The surfaces lining the pericardial cavity were smooth but were encased in the mass of tissue previously described. About 50 cc. of clear, amber fluid was present.

The heart and lungs were found to be as previously described. There were in addition underneath the visceral pericardium a few small, round, purple areas 1 or 2 mm. in diameter.

The spleen weighed 520 Gm. The capsule was thin and smooth. The cut surface was grayish purple and soft; the tissue could be scraped away with ease.

The liver weighed 1,380 Gm. The capsule was thin and the surface contour smooth. The liver was pale brown and soft. The gallbladder was normal.

The gastro-intestinal tract, pancreas, kidneys, suprarenal glands, urinary bladder, genital organs and aorta were normal on gross inspection.

In the femur the bone marrow was soft, cellular and a purple-red. The bone marrow of the vertebrae was dark red.

Microscopic Appearance: The lungs showed extensive infiltration with tumor cells. The type cell of the tumor was a cell which could be described as a small or intermediate-sized round cell presumably of the lymphoid strain. The nuclei were quite dark with chromatin, and the cytoplasm was small in amount. Mitotic figures were seen frequently.

The structure of the spleen and lymph nodes was masked by diffuse infiltration with the type cell. Mitotic figures were present in increased numbers. Occasional eosinophilic leukocytes were present.

The sinusoids of the liver were filled with the type cells. The periportal areas were infiltrated with the cells.

Normal bone marrow had been replaced by very hyperplastic tissue, chiefly composed of the round mononuclear cells previously described.

The other viscera showed the vessels and perivascular areas to be heavily infiltrated with tumor cells.

The microscopic diagnosis was lymphatic leukemia with mediastinal tumor (leukosarcoma).

Postmortem Cultures.—Cultures of the spleen and pleural fluid showed no growth.

COMMENT

In addition to the six cases of acute monocytic leukemia, the blood smears in three additional cases have been observed. One of these cases has been reported by Clough.[6] Another is to be reported subsequently.[8] The blood smears in each of these nine cases were very similar and in each the clinical history and physical examination revealed certain common characteristics.

Lesions of the Mucous Membranes as Aid in Differentiation of the Acute Leukemias.—It is my opinion that the clinical picture of diffuse, marked swelling of the mucous membranes, particularly of the gingivae usually with ulceration and necrosis, is characteristic of acute monocytic leukemia and is usually absent in acute leukemia of the myelogenous or lymphatic varieties. In association with these lesions of the mucous

8. Unpublished case in a Chinese to be reported from the Cheeloo University Medical School, Tsinan, Shantung, China.

membranes there occurs, usually, what appears to be a diffuse cellulitis about the lesions, causing swelling and pain with signs of acute inflammation extending into the deeper tissues of the face. Because of these presenting symptoms, all of the patients suffering from acute monocytic leukemia whose cases are reported in this communication consulted their dentists early in the course of their illness. It is true that patients with acute lymphatic leukemia and acute myelogenous leukemia frequently have symptoms referable to the mouth and other mucous membranes, but in my experience these lesions have been of a different sort and have been limited to hemorrhages and slight infection, and as a rule have not been characterized by diffuse swelling with ulceration and necrosis.

These differences in the clinical picture have not been appreciated heretofore. The impression conveyed in textbooks and in the papers on acute leukemia is that the symptoms are similar for all types, although all patients do not exhibit the same symptoms.

Of the twenty-three cases referred to by Clough [6] as probably authentic cases of monocytic leukemia, twenty-two have been reviewed in the present study with particular reference to the presence of lesions of the mouth. The report of the case by Sega and Brustolon [9] was not available for study. Of these twenty-two patients, eighteen had symptoms of marked stomatitis or pharyngitis with swelling of the gums, and in the majority ulceration, alveolar abscesses or sinus abscesses were present. Of the four remaining patients, one (Rosenthal [10]) had swelling of the neck but no reported lesions of the mucous membranes; a second patient (Ugriumow [11]) probably did not have acute monocytic leukemia but lymphatic leukemia with a mediastinal tumor (leukosarcoma); the third and fourth cases (Swirtschewskaja [12] and Lawrence, Josey and Young [13]) were of the subacute or chronic variety and therefore were not applicable to this study.

Eight additional cases, some of which were not accepted by Clough and others and were published subsequent to his study, have also been reviewed. The three cases reported by Ewald, Frehse and Hennig [14]

9. Sega, A., and Brustolon, A.: Leucemia monocitica o reticulo-endoteliosi leucemica? Haematologica, I. Arch. **10**:471, 1929.

10. Rosenthal, N.: Some Atypical Cases of Leukemia, M. Clin. North America **4**:1607, 1921.

11. Ugriumow, B.: Ein Fall von akuter Retikulo-Endotheliose, Centralbl. f. allg. Path. u. path. Anat. **42**:103, 1928.

12. Swirtschewskaja, B.: Ueber leukämische Retikuloendotheliose, Virchows Arch. f. path. Anat. **267**:456, 1928.

13. Lawrence, J. S.; Josey, A. I., and Young, M.W.: Three Cases of Monocytic Leukemia, Folia haemat. **44**:332, 1931.

14. Ewald, Frehse and Hennig: Akute Monocyten- und Stammzellenleukämien, Deutsches Arch. f. klin. Med. **138**:353, 1922.

in 1922, one additional case by Bingel [15] in 1916, one case by Dias [16] in 1930, one by Hittmair [17] in 1930 and two cases by Asselstine [18] in 1932 showed lesions of the mouth similar to those in the eighteen cases of acute monocytic leukemia. Other recent reports of cases by Muenzer,[19] Reich,[20] Lazzarini [21] and Invernizzi [22] were not available for study.

This analysis of the literature shows a striking uniformity in the lesions of the mucous membranes encountered in acute monocytic leukemia and is in agreement with my observations on this disease (table 4).

Other Physical Signs as Aids in Differentiation of the Acute Leukemias.—Not only do the symptoms and signs referable to the mucous membranes serve as aids in the differentiation of the acute leukemias, but there also exist other physical signs which, at least in adult patients, serve a similar purpose. It is usually true that the spleen, although somewhat enlarged, is not palpable in acute myelogenous leukemia, whereas in acute lymphatic leukemia the spleen is larger and is, almost without exception, palpable 2 or 3 cm. or even more below the costal margin. The spleen in acute monocytic leukemia, according to Clough, was palpable in sixteen of the twenty-four cases reviewed. In five of the six cases reported in the paper the spleen was easily palpable from 1 to 4 cm. below the costal margin. The weight of the spleen at autopsy in the first four cases reported in this communication was 1,065, 606, 360 and 900 Gm., respectively.

The size of the lymph nodes is also an aid in the differentiation of acute leukemia. It is my experience that usually, in fact almost invariably, there is a distinct general enlargement of the lymph nodes in acute lymphatic leukemia. This enlargement often is by no means as marked as that usually found in chronic lymphatic leukemia. The lymph nodes, particularly those in the neck, may be slightly or moderately enlarged in acute monocytic leukemia, but general enlargement to the extent found in acute lymphatic leukemia usually is not seen. It is even

15. Bingel: Monozytenleukämie? Deutsche med. Wchnschr. **42**:1503, 1916.

16. Dias, A.: Monocytose aiguë: Leucémie monocytaire, Rev. sud.-am. de méd. et de chir. **1**:41, 1930.

17. Hittmair, A.: Akute Myelose mit monozytoiden Zellformen, Folia haemat. **42**:271, 1930.

18. Asselstine, S. M.: Acute Monocytic and Lymphatic Leukemia, Canad. M. A. J. **26**:174, 1932.

19. Muenzer, J.: Monocytic Leukemia in Children, Polska gaz. lek. **8**:796, 1929.

20. Reich, C.: Monocytoid Myeloblastic Leukemia, New York State J. Med. **32**:1193, 1932.

21. Lazzarini, L.: Reticulo-Endotheliosis with Acute Leukemia, Osp. maggiore **18**:33, 1930.

22. Invernizzi, G.: Acute Monocytic Leukemia, Morgagni **73**:2329, 1931.

more uncommon to find generalized enlargement of the lymph nodes in acute myelogenous leukemia, and if any such enlargement is found it is slight (table 4).

TABLE 4.—*Clinical and Histologic Differentiation of the Three Main Types of Acute Leukemia*

		Acute Myelogenous Leukemia	Acute Lymphatic Leukemia	Acute Monocytic Leukemia
Spleen		Usually not palpable	Almost invariably significantly enlarged	Palpable in about 70 per cent of cases
Lymph nodes		Usually slight or no enlargement	General enlargement of moderate or marked degree	Moderate in neck, but other lymph nodes very slightly enlarged, if at all
Liver		Usually palpable	Usually palpable from 1 to 4 cm. below costal margin	Usually palpable from 1 to 4 cm. below costal margin
Mucous membranes, particularly of mouth and pharynx		Petechiae, bleeding; often slight swelling of gingivae but rarely ulceration	Petechiae, bleeding; rarely ulceration	Petechiae, bleeding; usually marked, diffuse swelling of gingivae or pharynx with ulceration; often cellulitis with swelling and tenderness of face; marked fetor oris
Histologic distinctions of type cells in blood and tissues	Oxidase reaction	From few to many oxidase-positive cells, with from few to many coarse granules	All lymphoid cells oxidase-negative	All monocytes positive or all negative, or some positive and others negative; positive cells contain relatively few fine granules
	Other characteristics	Dominant cells myelocytes "A" (Sabin) and myeloblasts; nuclei round or oval, usually with several nucleoli; cytoplasm deeply basophilic; myelocytes "B" (Sabin) present; Auer's bodies frequently present in few cells	Dominant cells lymphoblasts and young lymphocytes; nuclei round, oval or slightly indented, with few nucleoli usually present; relatively small amount of deeply basophilic, hyaline cytoplasm; mature lymphocytes present in fair number; occasional myelocytes "C" (Sabin) and metamyelocytes present	Dominant cells monoblasts and promonocytes; nuclei usually elongated and folded, deeply indented or otherwise irregular in contour; nucleoli rarely present; cytoplasm relatively abundant, usually not deeply basophilic and not hyaline but slightly basophilic and "ground glass-like"; Auer's bodies may be present in few cells; mature monocytes present in significant and varying numbers; myelocytes "C" and metamyelocytes often present in small numbers

Thus there are certain characteristic features in the history, symptomatology and physical signs which aid materially in the differentiation of the three main types of acute leukemia. These characteristics, in the

absence of a clearcut blood picture or of histologic studies on the tissues, are of value in establishing the diagnosis.

Hematologic Differentiation of the Acute Leukemias.—The cytologic aspects of the blood in acute leukemia are of great interest. This phase of the subject has been frequently discussed and well presented in many papers on the subject and need not be reviewed in detail in this communication. The definitive structural elements in the blood are readily classified, but when immature cells are found they frequently give rise to confusion, depending on the degree of immaturity. This confusion is enhanced in acute leukemia by a singular fact which does not occur in any other disease. The great majority, often more than 85 per cent, of the white blood cells in a given case of acute leukemia are of a uniformly immature type, usually in the myeloblast, monoblast or lymphoblast stage of development. Intermediate stages in the development of the type cell are therefore few and frequently do not permit safe deductions as to the type of cell by observation of intermediate phases in maturation. This difficulty is further accentuated by the fact that owing to the greatly disorganized hematopoietic system immature cells of strains other than that of the type cell may be present in small numbers in the blood. Hence one must rely on the finer cytologic characteristics of lymphoblasts, monoblasts and myeloblasts, and as all of these are sister cells derived from the same more primitive mesenchyme cells, their accurate differentiation is not always possible.

Sabin,[23] Simpson [24] and others have, in recent years, rediscovered a valuable method for the histologic study of blood and tissue cells. This so-called supravital technic is of particular value in the differentiation of the monocytic strain of cells and aids materially in the recognition of early myelocytes and their immediate precursors the myeloblasts. In certain cases it is only by a combination of all the available methods of study that an acceptable opinion concerning the type cell may be established. Certain other distinctly rare cases defy classification. The latter group, in the absence of other aids in the diagnosis, is usually regarded as stem cell leukemia or acute leukemia of undetermined type.

There are, however, commonly present certain distinctions in the cell types which have been illustrated in the accompanying drawings (fig. 1) of cells from the blood of patients with the three types of acute leukemia under discussion. The group of five cells illustrated in the upper left hand corner of the plate are from the blood of the patient

23. Sabin, F. R.: Studies on Living Human Blood Cells, Bull. Johns Hopkins Hosp. **34**:277, 1923.

24. Simpson, M. E.: Vital Staining of Human Blood with Special Reference to the Separation of the Monocytes, Univ. California Pub. on Anat. **1**:1, 1921.

EXPLANATION OF FIGURE 1

Fig. 1.—Cells from the blood of patients suffering from acute leukemia. The plate is divided into four sections: upper left, upper right, middle and lower. In these sections are colored camera lucida drawings of cells from the blood of four patients in the cases reported in this communication. The cells were stained by Wright's method and magnified 1,400 ×.

1. In the upper left hand corner are drawings of five white blood cells from the blood of the patient in case 7; the case was one of acute myelogenous or myeloblastic leukemia. The cells are myeloblasts and very early myelocytes (myelocytes "A" of Sabin).

2. The four white blood cells drawn in the upper right hand corner of the plate represent the dominant cells in the blood in case 2, one of acute monocytic leukemia. The cells are monocytes and premonocytes, possessing the characteristic nuclei and cytoplasm of such cells.

3. The nine cells represented in the middle section, right and left, are typical of those in the blood in case 1. The smallest of the cells is a small lymphocyte drawn for comparison. The other cells are monocytes in various stages of development. The large cell on the extreme left contains in its cytoplasm structures resembling Auer's bodies. The deeply basophilic cell on the extreme right is difficult to classify, but probably is an abnormal type of the monocytic strain of cells. The large cell just above the deeply basophilic cell is a young monocyte or premonocyte. The other cells represent later stages in maturation of monocytes.

4. The eight cells shown in the bottom section of the plate were found in the blood in case 8, one of acute lymphatic leukemia. The largest of these cells is shown in the process of mitosis. The smallest cell is an adult small lymphocyte. A typical polymorphonuclear neutrophilic leukocyte was drawn for comparison. The remaining five cells represent immature lymphocytes.

in case 7 (acute myelogenous leukemia) and illustrate the essential characteristics of myeloblasts. The nuclei are large, round, oval or slightly indented and contain several nucleoli. The cytoplasm is deeply basophilic and of uniform character. The four cells in the upper right hand corner belong to the monocyte series and were from the blood of the patient in case 2 reported in this paper. The five cells in the right middle section of the plate and the four in the left middle section were from the blood of the patient in case 1 (acute monocytic leukemia). All of them except the small lymphocyte in the left middle section represent various forms of monocytes, premonocytes and monoblasts. The nuclei for the most part tend to have a complicated shape and possess very few nucleoli. The cytoplasm is relatively abundant, is generally less basophilic and contains many dustlike granules. One of the cells contains several elongated reddish structures (Auer's bodies) in the cytoplasm. The large deeply basophilic cell on the right is presumably a very young monoblast or possibly an atypical premonocyte. The eight cells occupying the bottom one third of the plate were from the blood of the patient in case 8 (acute lymphatic leukemia). One of these cells is a definitive young lymphocyte, another a polymorphonuclear neutrophil and another a large lymphoid cell in the process of mitotic division. The other five cells are immature lymphocytes; they have large nuclei with diffuse chromatin distribution and a relatively small amount of hyaline, moderately basophilic cytoplasm.

Histologic Differentiation of the Acute Leukemias.—Just as the clinical and hematologic differentiation of the acute leukemias is often difficult and doubtless frequently incorrectly made, so it is also with the pathologic differentiation. The chief criterion on which the pathologist relies is the oxidase reaction of the tissues. If the cells infiltrating the liver, kidney and other tissues are oxidase-positive and if the architecture of the blood-forming organs is disorganized and shows indiscriminate hyperplasia of uniformly immature cells, the diagnosis of myelogenous leukemia is made. On the other hand, if such a state exists, but without a positive oxidase reaction, the diagnosis of lymphatic leukemia or of lymphoblastoma is in order.

With the discovery of a third type of leukemia—monocytic—the pathologic diagnosis becomes more difficult, because in this type the oxidase reaction of the tissues or of the blood cells may be either positive or negative, and hence the chief point for the differential diagnosis is lost. There are, however, certain characteristics of the histology which are of great importance, which are little appreciated and which usually are distinctive. Although often it is extremely difficult or impossible in good paraffin sections to distinguish lymphoblasts from myeloblasts, this is not true of monocytes and their precursors. The

latter cells, when observed by means of the oil immersion lens in the blood or in their sites of formation in the tissues, have certain characteristics distinguishing them from myeloblasts or lymphoblasts. The nuclei, even of premonocytes and of monoblasts, are usually of irregular shape, often in the form of an irregular crescent or a broad elongated nucleus bent on itself. Frequently the nucleus is bent on itself several times, giving the impression of lobulation, although distinct separation of the lobules is rarely demonstrable in contrast to the characteristic nucleus of the polymorphonuclear granulocyte. There exist also many young cells of the monocyte series which have simple round, oval or slightly indented nuclei, but these cells exist as close companions of the cells with the more complicated nuclei as described. Furthermore, other characteristics distinguish the monocytic cells from the early lymphoid and myeloid elements. The nuclei of the monocytic series of cells rarely have demonstrable nucleoli, whereas these structures are very common in lymphoblasts and myeloblasts. The cytoplasm of premonocytes and monoblasts is, as a rule, more abundant and much less basophilic than that of either lymphoblasts or myeloblasts and frequently is so faint, with hematoxylin and eosin or with eosin-methylthionine chloride, U. S. P. (methylene blue) stains, that the border of the cell is barely recognizable. This appearance is in contrast to the moderate or very deep basophilia of early lymphoid and myeloid cells.

There has been much controversy concerning the existence or absence of granules in monocytes giving a positive reaction to oxidase or peroxidase staining. Certainly it is true that the great majority of the normal monocytes in human blood when stained with the copper sulphate-benzidine-peroxide-safranin method of Sato and Sekaya do possess blue granules, similar to but not identical with those in neutrophilic myelocytes. This is in contrast to the total absence of such granules in all the cells of the lymphoid series. It appears also to be true that a few perfectly definite monocytes in the blood of normal persons and frequently many of the early monocytes in pathologic states may possess no such granules. When present the oxidase or peroxidase granules in monocytes are smaller and fewer than those encountered in myelocytes, and this characteristic at times is useful as an aid for differentiation.

The essential destruction of the normal architecture of the hematopoietic organs and its replacement by a disordered hyperplasia of immature blood cells is then a characteristic of all types of leukemia. Careful studies of the oxidase reaction and of the character of the type cells dominating the picture is essential for histologic differentiation of the three main types of acute leukemia.

Origin of the Monocyte.—No subject in hematologic literature has been the source of more controversies than this much disputed question. There exist no less than nineteen separate views on the origin of the monocyte (fig. 2). Fibroblasts, primitive undifferentiated cells, lymphoid cells, the endothelium of the blood vessels, reticulo-endothelial cells, myeloblasts and various miscellaneous cells have all been claimed to be the mother cells of monocytes. Many of these views have been obtained from the study of the diseased tissues. It is fair to say that in normal man the development of monocytes in the blood-forming tissues has never been demonstrated. In animals in no organs or tissues, other than in certain lymph nodes, chiefly the peripheral group, can one find constantly monocytes in all stages of development.[25] In these lymph nodes they have been shown to arise from primitive undiffer-

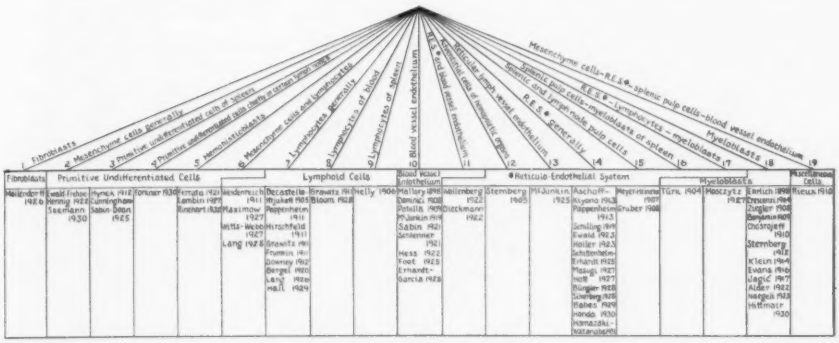

Fig. 2.—Theories of the origin of monocytes.

entiated cells going through the stages of monoblasts and premonocytes to definitive monocytes.[25]

It was hoped that a study of these cases of monocytic leukemia would throw some light on the origin of the monocyte in man. However, since all the hematopoietic tissues, as in the other types of acute leukemia, were crowded with the type cells, no conclusions as to origin were possible.

SUMMARY AND CONCLUSIONS

Eight cases of acute leukemia are presented, six of acute monocytic leukemia and one each of the acute myelogenous and acute lymphatic types.

25. Forkner, C. E.: Material from Lymph Nodes: IV. The Heterology of Lymphoid Tissue with Special Reference to the Monocyte; Supravital Studies, J. Exper. Med. **49**:323, 1929; The Origin of Monocytes in Certain Lymph Nodes and Their Genetic Relation to Other Connective Tissue Cells, ibid. **52**:385, 1930.

The three main types of acute leukemia, contrary to accepted belief, have certain distinctive clinical features.

Attention is directed particularly to the symptoms and signs referable to the upper alimentary and respiratory tracts and those associated with hyperplasia of the hematopoietic tissues.

Certain histologic differences exist in the blood and tissue cells which are diagnostic of the various kinds of acute leukemia.

This study has been confined mainly to acute leukemia in adult patients and, therefore, in some respects may not be applicable to this disease as it occurs in young children.

These studies were made in Dr. George R. Minot's laboratory. Dr. Frederick Parker, Jr., aided in the pathologic study.

CARDIAC OUTPUT

ITS RELATED FUNCTIONS IN A CASE OF COARCTATION OF THE AORTA

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AND
J. P. FERRIGAN, JR., A.B.
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Coarctation of the aorta presents several features of interest concerning the hemodynamics and regulation of the circulation, for it presents a condition in which the brain and carotid sinus, the chief sites of any central regulatory functions, are subjected to an arterial hypertension while the lower extremities and viscera are supplied with blood at a lower pressure. The cardiac output has not hitherto been studied in cases of coarctation. Because of the relative infrequency with which the condition is recognized in young persons before the advent of secondary complications, and because of the interesting theoretical considerations involved, the results obtained in a single person have been considered worthy of a report.

REPORT OF A CASE

Clinical History.—The subject of our study, J. P. F., Jr., was a medical student, 25 years of age. His family and past history were entirely irrelevant. Except for diphtheria, measles, chickenpox and occasional colds, his health had always been good.

In the course of a routine physical examination in January, 1924, he was told that he had "chronic endocarditis." At that time he was pursuing an active life, engaging in athletics and had suffered no discomfort. The examination revealed a systolic blood pressure of about 185 mm. but the test was taken in only one arm. This diagnosis was confirmed by several physicians. The patient was put on a low protein and low salt diet and was ordered to have complete quiet and rest.

At the end of two months, this regimen was relaxed. The diet was gradually returned to normal and more activity was permitted in the course of the next two and one half years, during which time he was constantly under the observation of a physician. There was no apparent change in his condition, except a slight decrease in the systolic blood pressure as taken in either the right or the left arm.

In October, 1931, he entered medical school. In the course of a routine physical examination a roentgenogram showed scalloping of the inferior borders of the ribs; and a diagnosis of coarctation of the aorta was made by Dr. Charles C. Waters.

Subsequent examinations by Dr. John T. King, Jr., and Prof. Warfield T. Longcope confirmed this diagnosis and showed the presence of the other diagnostic

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signs of the adult type of coarctation,[1] such as higher blood pressure in the arms than in the legs, bilateral pulsations in the interscapular region and systolic murmur along the vertebral borders of the scapulae. There were also signs of aortic insufficiency, indicative of the presence of some defect of the aortic valves which occurs commonly in cases of coarctation.[1]

Subjectively the patient manifested no signs of incompetence of the cardiovascular system. He engaged in severe exercise (tennis and swimming) with no discomfort, and was otherwise free from symptoms (the claudication of the lower extremities, abdominal distress) encountered in this condition. Analysis of the urine showed it to be normal; the hemoglobin content was 120 per cent, with an erythrocyte count of 5,600,000.

Experimental Findings.—The cardiac output was determined by the acetylene method on two separate occasions. Duplicate determinations were made in the basal resting condition as prescribed in detail elsewhere.[2] The cardiac output was 4.8 and 5 liters, an average value of 4.9 liters, with an average arteriovenous oxygen difference of 61 cc. per liter. Although this arteriovenous difference is within the range of normal values found in persons of the age of the patient, the cardiac output was higher than is normal, owing to the elevated oxygen consumption. This was reflected in a high cardiac index. The patient's height was 180 cm. and his weight was 77 Kg. His surface area was 1.96 square meters as calculated by DuBois' formula.[3] Therefore, his cardiac index was 2.5 liters per square meter of body surface, which is approximately 15 per cent above normal.

The elevated cardiac index observed in our subject in the presence of a normal arteriovenous oxygen difference is similar to that observed in hyperthyroidism and is a concomitant of the elevated oxygen consumption.[2] The increased cardiac output might thus be looked on as secondary to the increased metabolism and not as incident to the anatomic defect of the aorta. It differs thus from the increased cardiac output observed in cases of benign hypertension.

Blood Pressure.—The arterial blood pressures in the extremities were measured by the Tycos recording sphygmomanometer. The values obtained with the patient in the recumbent position were as follows: right brachial artery, 162 systolic and 81 diastolic; left brachial artery, 176 systolic and 98 diastolic; right femoral artery, 109 systolic and 80 diastolic; left femoral artery, 113 systolic and 78 diastolic. The high pulse pressure in the arms is explicable on the basis of the relatively free anastomoses present, which would allow a sudden outflow of blood from the arterial system and be equivalent to a marked reduction of the peripheral resistance.

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1. Abbott, M. E.: Coarctation of the Aorta, in Osler, William, and McCrae, Thomas: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 772. Blackford, L. M.: Coarctation of the Aorta, Arch. Int. Med. **41**:702 (May) 1928. Eppinger, E. C., and Midelfart, P. A. H.: Stenosis of the Isthmus (Coarctation of the Aorta), Am. J. M. Sc. **185**:528, 1933. Evans, W.: Congenital Stenosis (Coarctation), Atresia, and Interruption of the Aortic Arch, Quart. J. Med. **2**:1 (Jan.) 1933. King, J. T., Jr.: Stenosis of the Isthmus (Coarctation) of the Aorta and Its Diagnosis During Life, Arch. Int. Med. **38**:69 (July) 1926.

2. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

3. DuBois, E. F.: Basal Metabolism in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1927.

In this patient, part of this excessively high pulse pressure may be attributed to the existence of the aortic insufficiency described.

The basal pulse rate varied from 80 to 84. Thus, the systolic output was 60 cc., which is the normal average.[2] The increase in pulse rate observed in the patient was, therefore, proportional to the increased cardiac output and resulted in the maintenance of a normal output per beat.

The cardiac work was increased in our subject as a result of the increase in its capacity factor (the cardiac output) as well as the increase in arterial tension against which the heart was laboring. The observed cardiac hypertrophy (a minor degree of which was already present in the patient) is thus attributable to this overwork, and the ultimate development of decompensation in coarctation is to be expected on the same basis as it occurs in other conditions, e. g., in hyperthyroidism, accompanied by a long-continued overworking of the heart. The overwork in our patient was occasioned, however, by two factors: the increased demands occasioned by an elevated metabolic rate and the mechanical effect of expelling this increased amount of blood against an elevated arterial pressure, necessitated in order to supply the lower part of the body with blood and to overcome the effects of the aortic insufficiency.

The metabolic rate of our patient was definitely elevated. The oxygen consumption measured on three occasions at weekly intervals was 300, 306 and 308 cc. per minute, an average of 305 cc. His oxygen consumption, calculated according to the Aub-Dubois standards (39 calories per square meter of body surface),[3] was 265 cc., corresponding to a basal metabolic rate in the patient of +15 per cent.

Little attention has been paid in previous studies to the basal metabolic rate in patients with coarctation of the aorta, although it has been reported as elevated in several cases. It is interesting to note that such patients are sometimes considered to be suffering from hyperthyroidism. Although this confusion has been attributed to the warm and suffused condition of the skin of the face and upper extremities, it is possible that the actual existence of a moderate degree of hyperthyroidism may be in part responsible for the confusion noted.

Although it is hazardous to draw conclusions from a single study, it may be sugggested that an abnormally active circulation (due to the hypertension) through the thyroid gland might lead to a hyperemia of this organ with a consequent physiologic hyperactivity. It is interesting to note in this connection, too, that approximately 20 per cent of the patients with essential hypertension studied by Boothby and Sandiford [4] exhibited a basal metabolic rate of over + 10 per cent. Whether our patient whose case is reported belongs to this group as regards the etiology of his elevated basal metabolic rate is problematic.[5]

4. Boothby, W. M., and Sandiford, I.: Basal Metabolism, Physiol. Rev. **4**:69, 1924.

5. In a recent paper, H. L. Ulrich (Am. Heart J. **7**:641, 1932) reported hyperthyroidism in two of his three cases of coarctation of the aorta of the adult type. He offers an explanation similar to that just discussed to explain the cause of this hyperactivity of the thyroid. Ligation of the inferior thyroid arteries, as suggested by Ulrich, would not only relieve the symptoms of hyperthyroidism, but would also reduce the basal cardiac work and thus relieve the extra myocardial strain to which patients with an elevated metabolism are subjected.

COMMENT

The findings are in accord with what might be anticipated from the clinical state of our patient. His heart is capable of overcoming the anatomic defects by expelling its blood at a high pressure which, in the presence of an adequate collateral circulation, permits a normal supply of blood to the entire body. There is probably an excessive supply to the head and the upper extremities. This is balanced by an approximately equal (as judged from the value of the cardiac output) diminution of blood supply to the lower part of the body.

Our observations are in accordance with the finding of a normal arteriovenous oxygen difference in the legs of a patient with coarctation by Blumgart, Lawrence and Ernstene.[6] Our findings obviously speak against the view that the pressure in the carotid sinus or in other central regulatory mechanisms exerts any considerable influence on regulation of the cardiac output. Were this the case, one would expect a diminished output in coarctation of the aorta. On the other hand, the normal value of the arteriovenous oxygen difference in our patient indicates this to be the more fundamental factor in controlling the circulation. The metabolic needs of the integral parts of the entire body determine their circulatory supply of blood, and the cardiac output responds to this demand.[2]

6. Blumgart, H. L., Lawrence, J. S., and Ernstene, A. C.: The Dynamics of the Circulation in Coarctation (Stenosis of the Isthmus) of the Aorta of the Adult Type, Arch. Int. Med. **47**:806 (May) 1931.

MYASTHENIA GRAVIS

THE EFFECT OF TREATMENT WITH GLYCINE AND EPHEDRINE; THIRD REPORT

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It is unnecessary to review the history of the recognition of myasthenia gravis as a clinical syndrome or to enter into details concerning the symptoms, course and prognosis of the disease. The variations in intensity are well known, as are the inconstancy in the rapidity with which the characteristic symptoms of the disease progress, the frequency of the partial remissions during slow but certain progression to a fatal issue and the rarity of complete intermission or spontaneous cure. It may not be generally realized that the disease is by no means rare; that the early stages, sometimes lasting for years, are often overlooked, and that the condition is recognized only in the later stages, which are followed rather rapidly by death, hastened by inhalation pneumonia and inanition.

The etiology of myasthenia gravis is not known. The evidence, however, substantiates the idea that the weakness accompanying the disease is due to disturbance of the intermediate chemical reactions concerned with muscular contraction, or to recovery therefrom. The fact that certain groups of muscles having a more or less common innervation are involved leaves the possibility open that the trophic nerves are in some unknown way involved in the syndrome. The frequency of a history of a sore throat or respiratory infection preceding the first attack may be significant.

No method of treatment of this disease proved of avail until Edgeworth [1] accidentally discovered the value of ephedrine for this purpose.

The second step in advance in the treatment of myasthenia gravis has resulted from the use of glycine. The possibility that glycine might prove beneficial was suggested by the report of Thomas, Milhorat and

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From the Section on Clinical Metabolism, the Mayo Clinic.

Read before the Association of American Physicians, Washington, D. C., May 9, 1933.

1. Edgeworth, Harriet: A Report of Progress in the Use of Ephedrine in a Case of Myasthenia Gravis, J. A. M. A. **94**:1136 (April 12) 1930; The Effect of Ephedrine in the Treatment of Myasthenia Gravis: Second Report, ibid. **100**: 1401 (May 6) 1933.

Techner [2] on its favorable action in progressive pseudohypertrophic muscular dystrophy. I have made two reports [3] on the results obtained by the use of glycine and ephedrine. Remen [4] has also reported on the beneficial effects of administration of glycine to patients with myasthenia gravis.

Glycine is one of the simpler amino-acids, and therefore, is one of the constituents of most proteins, including muscle protein. Since our bodies have, under normal conditions, the ability to synthesize this substance, it is probable that the substance is exceedingly important for many different purposes. Just how it is beneficial in myasthenia gravis is not known; neither is it known why or how ephedrine produces a beneficial effect. Much also remains to be learned about the early diagnosis as well as the ultimate prognosis of this disease.

In the last year, in the Mayo Clinic twelve patients with myasthenia gravis have been closely observed, and personal reports on about as many more who have been treated elsewhere gave the information that a large proportion have improved definitely.

All the cases I observed can be accepted as typical and true examples of the disease, as the diagnosis was corroborated by several members of the Section on Medicine and by the members of the Section on Neurology of the clinic. The disease varied in intensity, and for the purpose of brief presentation the twelve cases may be placed in four groups, depending on the severity of the condition at the time the patients came under observation. Seven of the patients were men and five were women.

GROUPS OF CASES

Group 1 (Four Cases).—Two of the patients were men and two were women. The chief weakness exhibited by this group was in the muscles of deglutition; there was only slight weakness in the muscles of the extremities. The patients were all able to be up and about, but they had difficulty in eating solid food and were troubled with a consid-

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2. Thomas, Karl; Milhorat, A. T., and Techner, Fritz: Untersuchungen über die Herkunft des Kreatins. Ein Beitrag zur Behandlung progressiver Muskelatrophien mit Glykokoll, Ztschr. f. physiol. Chem. **205**:93, 1932. Milhorat, A. T.; Techner, Fritz, and Thomas, Karl: Significance of Creatine in Progressive Muscular Dystrophy and Treatment of This Disease with Glycin, Proc. Soc. Exper. Biol. & Med. **29**:609 (Feb.) 1932.

3. Boothby, W. M.: Myasthenia Gravis: A Preliminary Report on the Effect of Treatment with Glycine, Proc. Staff Meet., Mayo Clin. **7**:557 (Sept. 28) 1932. Boothby, W. M.; Adams, Mildred; Power, M. H.; Edgeworth, Harriet; Moersch, F. P.; Woltman, H. W., and Wilder, R. M.: Myasthenia Gravis: Second Report on the Effect of Treatment with Glycine, Proc. Staff Meet., Mayo Clin. **7**:737 (Dec. 28) 1932.

4. Remen, L.: Zur Pathogenese und Therapie der Myasthenia gravis pseudoparalytica, Deutsche Ztschr. f. Nervenh. **128**:66, 1932

erable quantity of the thick mucus in the larynx, which is a more or less characteristic accompaniment in the so-called bulbar type of the disease. The two men had marked ptosis of the eyelids and weakness of the muscles of the eyeball. One of the men and one of the women had been treated with ephedrine ⅜ grain (0.02 Gm.), two or three times daily, for more than a year before their admission to the clinic. At first the ephedrine had caused considerable improvement; this, however, was not maintained. With the addition of glycine in doses, varying between 20 and 30 Gm., further improvement resulted. At the time of writing, eight months later, the man, aged 64, is in good condition; he is able to work and to eat without much difficulty. The woman, aged 35, is able to continue her work as a secretary. During the last two or three months they have been able materially to decrease the amount of ephedrine and of glycine taken daily, without any aggravation of symptoms.

The other two patients, a man aged 69 and a woman aged 37, started treatment at about the same time. The dosage was ephedrine, ⅜ grain twice daily, and glycine, 30 Gm. daily. The man is in good condition for his age, and during the winter successfully passed through two severe colds. The woman has been able to continue her work as a secretary without much difficulty. During the last two or three months both have required less glycine and less ephedrine.

Thus the condition of these four patients has improved definitely, and although they cannot be considered cured, they are able to carry on their lives in a reasonably comfortable and happy manner.

Group 2 (Five Cases).—In this group, weakness of the muscles of deglutition was marked; the muscles of the extremities were also weak. All the patients had difficulty in chewing and swallowing, trouble with mucus, and ptosis of the eyelids; they were able to walk only a short distance alone without falling.

One of the patients, a man aged 38, who was given ephedrine, ⅜ grain twice daily, and glycine, 30 Gm. daily, improved greatly. From being unable to walk a block alone, he now walks 5 or 6 miles, rests ten or fifteen minutes and then walks back. He can run several blocks. One day he shoveled snow for two hours without undue fatigue. He has regained normal strength in his arms and hands. He eats without difficulty. In the last few months he has taken much less glycine and ephedrine; but he found that if he reduced the doses below a certain amount he became weaker.

The second patient, a man aged 56, was even weaker at the time of examination than the first patient, in part due to loss of weight as a result of difficulty in swallowing. He was given ephedrine, ⅜ grain twice daily, and glycine, 15 Gm. twice daily. His condition remained

stationary for three weeks, then started to improve rapidly. At the end of four months he had gained about 40 pounds (18.1 Kg.), was able to walk eight or ten blocks, and to carry on relatively light work as an electrician for a public service corporation. He, too, has been able to reduce the amount of glycine and ephedrine required to maintain his strength.

The third patient was a man, aged 38, who was unable to walk alone more than one or two blocks and who had moderate difficulty in swallowing. In two months this patient was able to return to his work as a driver of a laundry delivery truck throughout the cold winter. His treatment started with a dose of 30 Gm. of glycine daily. Ephedrine was tried for three days only; it made him worse; so it was discontinued. Recently he has been reducing the amount of glycine until now he takes about 10 Gm. daily. In a letter received a week before this article was written he urgently requested that more glycine be sent quickly, as his supply was low and he was becoming quite weak on a reduced dose. We have not yet heard of the effect of again increasing the dose.

The fourth patient was a schoolgirl, aged 18, who was able to walk only a block or two with the support of her mother's arm. She had difficulty in swallowing and was particularly troubled with mucus. She received both glycine and ephedrine in the usual doses and regained strength rapidly. She is now able to resume her school work, and to lead a reasonably normal life. Usually, however, just before her menstrual period she is barely able to carry on her school work.

The last patient in this group was a woman aged 79. She was very weak, was unable to be out of bed, and had great difficulty in eating. She was given ephedrine for two months and her condition improved definitely; it then seemed to become stationary. Glycine was added to the treatment, and further improvement occurred. The patient is now able to eat soft foods easily, has little mucus, is up and about her room for several hours a day, and occasionally goes outdoors.

Group 3 (One Case).—The patient in this case is Dr. Edgeworth, with whose long fight against myasthenia gravis all are undoubtedly familiar. As is known, she discovered the value of ephedrine in the treatment of this disease. As the result of her skilful treatment of her own condition with ephedrine she was able to transform herself from a bedridden patient to a person able to carry on a reasonably active life. She can walk short distances; she eats well and, except at menstrual periods, she is up and about the house and garden all day and can travel extensively. During the last six months she has also been taking glycine, but has not observed marked alteration in the rate of improvement, which has been steady, although, slow, during the last two years.

Group 4 (Two Cases).—The two men in this group, aged 43 and 24 respectively, did not respond as favorably as the others, either to glycine or to ephedrine during a period of four or five months. One of the patients came to the clinic in the latter part of December, 1932. The first definite symptoms had occurred a month previously; prodromal symptoms could be traced back another six months or more. The disease was in a rapidly progressing stage; each day the condition was noticeably worse. The patient was barely able to walk and he swallowed with great difficulty. Glycine, in doses of 30 Gm. daily, was started on January 4, and ephedrine, 3/8 grain twice daily, on January 16. Slight improvement was noted on January 18, when the patient insisted, against advice, on riding to South Dakota to attend to business. He returned a week later very much worse, and was having rather frequent attacks of marked dyspnea. The cause of this dyspnea was not determined until January 30, when I found him on the floor in a knee-chest position with a "crooning" respiration. Examination disclosed a large flabby epiglottis hanging down over the larynx and acting as a flap valve. Tracheotomy relieved the obstruction, but the respiratory muscles had become so exhausted in the struggle that artificial respiration by manual methods was necessary while he was being placed in the Drinker respirator. He was in the respirator twenty-two days; after the first eight days he could dispense with the respirator an increasing number of hours each day. He was fed by a Rehfuss tube through the nose.

By March 9 the patient had improved sufficiently to go to an apartment in town. He was up and about the room each day. He breathed easily through the tracheotomy wound and was still given nourishment through the Rehfuss tube. He caught cold and the favorable progress was halted, and finally a slow, gradual decline set in. He became nervous, irritable, and hard to feed; he gave up all hope of recovery and refused to co-operate in the treatment, although the degree of muscular weakness was by no means as marked as at the previous low point. He continued to receive glycine and ephedrine in practically the same doses; moderate variations in dose caused no demonstrable change. In the hope that insulin might be beneficial this was given for a few weeks, in doses increasing to 40 units, but without benefit. Also, in the hope that the administration of creatine would be beneficial, this was given in 1 Gm. doses for a week. The ingested creatine was largely but not entirely excreted during this time, which was in contrast to the little that was excreted following a single dose before the treatment with glycine was started. During the period in which creatine was administered the patient became more nervous, irritable, less co-operative and despondent. He died on April 27, 1933, from causes not directly attributable to the myasthenia syndrome.

Dr. Robertson made a detailed postmortem examination, and I include a brief abstract of his report. The postmortem examination did not reveal thymic or suprarenal tumor, or other gross abnormality. The brain, cord and nerve fibers were not demonstrably abnormal. The muscles, particularly of the thorax and extremities, were fully developed and had a good color. The muscles around the larynx were definitely atrophic and pale. Microscopic examination of these muscles disclosed patchy or interstitial atrophy of the fibers, and infiltration with lymphocytes and reticular cells. Degenerative or fatty changes in the fibers were not outstanding. The muscles of the thoracic wall and diaphragm were much less involved than those of the larynx. In the cortex of the kidneys there were eleven small nodules, about 2 to 4 mm. in diameter, which were composed of masses of lymphocytes with a center core of eosinophils. Parasites, necrosis or other significant changes could not be observed in these nodules. The cultures of the muscles and of the blood in the heart were uniformly negative.

The second patient in this group had had what was apparently an unrecognized mild attack several years ago from which he had almost completely recovered. In the last year the symptoms recurred and recently quite rapidly. On his arrival at the clinic about Feb. 14, 1933, he presented the typical symptoms of severe progressing myasthenia gravis with marked difficulty in swallowing and weakness of the extremities. For several weeks he had been confined to bed during the greater part of the day, and had been taking ⅜ grain of ephedrine from three to four times daily. During his first twenty days at the clinic the nitrogen balance was determined. He was rapidly losing weight, and was in definite negative nitrogen balance. Before treatment with glycine was started, the negative nitrogen balance was about 3 Gm. daily, and even with the addition of 30 Gm. of glycine daily the nitrogen balance still remained negative to about the same extent. In spite of treatment, difficulty in swallowing became so great that the patient was fed by a Rehfuss tube in the hope of giving enough food to decrease the negative nitrogen balance. It was impossible to determine the nitrogen balance again, but since after intake of food was increased the general condition did not become materially worse, the negative nitrogen balance probably decreased. In the last three months the patient's condition has shown slight fluctuation, but with no definite trend in either direction.

SUMMARY

Of twelve patients with myasthenia gravis treated with ephedrine and glycine, ten have shown definite improvement; four of these have shown marked improvement. Two did not respond to treatment except that the progress of the disease was apparently arrested; one of the two died from causes not directly attributable to the myasthenic syndrome.

I feel sure that by the careful use of either ephedrine or glycine, and more often of both, the condition of most patients with myasthenia gravis can be improved sufficiently to permit them to return to work or at least to enjoy a useful life. Time alone will tell whether this improvement can be maintained. The disease occurs much more frequently than is generally supposed.

ABNORMALITIES OF CALCIUM DEPOSITION IN DIABETES MELLITUS

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The occurrence in the George F. Baker Clinic recently of two cases of compression "fractures" or crushing of the vertebrae with generalized decalcification of bones focused our attention anew on the question of calcium metabolism in diabetes. The subject is of importance both to doctors and to patients. Thus, one of the patients referred to made her illness the basis of a lawsuit in which she sued a physician in her home city, maintaining that improper treatment of the diabetes was the cause of her disability. The importance of information as to the incidence of decalcification of bone in diabetes is obvious. The possibility also exists that with a growing tendency in some clinics, both in America and abroad, toward the use of diets extremely low in fat, cream may be withdrawn from the dietary, and it may be forgotten that unless milk, whole or skimmed, is supplied, the calcium requirement of the body will probably not be met. A lack of calcium can prove serious both for the aged and for the growing child.

REPORT OF CASES

CASE 1.—A Jewish housewife, 62 years old, with diabetes of ten years' duration, was admitted to the New England Deaconess Hospital on Sept. 9, 1932, because of backache of eight months' duration. Physical examination showed signs of loss of weight and advanced kyphosis with marked tenderness and hyperesthesia of the skin over the spine and muscles lateral to it in the lower dorsal and upper lumbar region. Roentgenograms revealed generalized decalcification of bones with crushing of the seventh and eight dorsal and first lumbar vertebrae. No evidence of a malignant condition was found. The arteries of the arms and legs showed a high degree of calcification, as did the descending aorta. The blood serum calcium was 10 mg., and the phosphorus, 3.7 mg., per hundred cubic centimeters.

CASE 2.—An Irish housewife, 77 years of age, with diabetes for eighteen years, entered the New England Deaconess Hospital on Nov. 8, 1932, because of persistent pain in the back which had been present for three days following a minor jolt in an automobile. For ten years she had lived alone, preparing her own meals; she stated, however, that she had drunk a quart of milk a day for years.

From the George F. Baker Clinic, Director, Elliott P. Joslin, M.D., New England Deaconess Hospital, Boston.

Physical examination on admission showed marked tenderness over the middle of the back. Roentgenograms showed generalized decalcification of the bones with a compression fracture of the fifth thoracic vertebra. There was visible calcification in the arteries of the extremities and in the aorta. The blood serum calcium was 9.4 mg., and the phosphorus, 2.8 mg., per hundred cubic centimeters on Nov. 10, 1932. On December 5, after almost a month of administration of calcium gluconate and viosterol, these values were 10.5 mg. and 3.8 mg. per hundred cubic centimeters, respectively. On December 5 the total protein of the blood serum was found to be 7.6 Gm. per hundred cubic centimeters.

Treatment in both cases was carried out with the advice of Dr. Mark H. Rogers. It consisted at first of rest in bed with hyperextension and the subsequent use of braces, combined with a diet high in calcium, calcium gluconate and viosterol. Partial relief from pain and gradual return to greater activity were obtained in both instances. Roentgenograms of the bones will be taken at intervals in an effort to demonstrate deposition of calcium. It is interesting that in case 1, despite clinical improvement, films taken on April 21, 1933, seven months after the first roentgenograms were taken, showed no change.

FREQUENCY OF OSTEOPOROSIS IN DIABETES

These two cases are the only instances of osteoporosis with crushing of the vertebrae which have been recognized among 12,000 patients who have applied for diagnosis or treatment of diabetes over a period of thirty-five years. Except for the report of Morrison and Bogan,[1] who found delayed development of bone, narrowness of the shaft and thinness of the cortex with atrophy of the bone in some cases of diabetes in children, no systematic study of roentgenograms of bones of persons with diabetes is known to us. At present no accurate statement is possible as to whether or not decalcification of bone is more common in persons with diabetes than in persons without diabetes. In any such comparison, proper attention must be given to the age of the patient, his activity and the amount of calcium in his diet.

It is true that in some patients fractures have seemed to occur with slight trauma. For example, one patient, while alternately raising and lowering his feet on a bath mat, felt a sudden pain in one foot; a roentgenogram showed a fracture of the second metatarsal bone. Another, aged 28 years, with diabetes of two years' duration, undergoing extreme undernutrition, fell from a low bed and fractured a rib. She began treatment with insulin in December, 1922, and is now in excellent condition. When in the hospital a patient while walking slipped to the floor (covered with a rubber flooring material) and fractured his skull. Another patient, while walking, turned his ankle and fell, striking the

1. Morrison, L. B., and Bogan, I. K.: Bone Development in Diabetic Children: A Roentgen Study, Am. J. M. Sc. **174**:313 (Sept.) 1927.

side of his left hand on the floor, thereby fracturing the fifth metacarpal bone. At the autopsy of another person, who died at the age of 54 years with diabetes of seven months' duration, the ribs were found to be so fragile that they could be snapped in two between the thumb and two fingers. Other known cases of fractures which followed greater trauma have not been cited, because our data do not allow an accurate statement as to the incidence of broken bones in the general diabetic series.

Although only one case cited occurred in the period before treatment with insulin, in every case diabetes had existed for long periods without treatment with insulin or adequate dietary treatment, so that it is probable that these patients had suffered from mild acidosis or incompletely controlled diabetes at intervals over a prolonged period. It is well recognized that in diabetic acidosis, as in acidosis due to other causes, there is an increased excretion of calcium in the urine. This was early demonstrated by Joslin [2] and substantiated by careful recent work such as that by Atchley and his associates.[3]

From a review of the older literature one would infer that in diabetes mellitus in general there is an increased excretion of calcium. Thus, von Noorden [4] mentioned that such findings were reported by Böcker, Neubauer, Toralbo, Gerhardt, von Moraczewski, and others, including workers in his own laboratory. Falta and Whitney,[5] from experiments on depancreatized dogs, believed that the negative calcium balance and the calcium excretion which were observed were out of proportion to any degree of acidosis present. Somewhat more recently (but still before the time when strict control of diabetes by insulin became possible) Kahn and Kahn [6] found a definite negative calcium balance in all of five cases studied.

Although in this clinic the incidence of fractures has been low, other instances of faulty calcium deposition have been noted. Dental consultants state that on the whole the teeth of our children whose diabetes is well controlled with diet and insulin show no abnormal incidence of dental caries, whereas children with diabetes who have

2. Joslin, E. P.: Metabolism in Diabetic Coma, with Especial Reference to Acid Intoxication, J. M. Research **6**:316 (Nov.) 1901.

3. Atchley, D. W.; Loeb, R. F.; Richards, D. W. Jr.; Benedict, E. M., and Driscoll, M. E.: On Diabetic Acidosis. A Detailed Study of Electrolyte Balances Following the Withdrawal and Reestablishment of Insulin Therapy, J. Clin. Investigation **12**:297 (March) 1933.

4. von Noorden, C.: Metabolism and Practical Medicine, Chicago, W. T. Keener & Co., 1907, vol. 3, p. 600.

5. Falta, W., and Whitney, J. L.: Zur Kenntnis des Eiweiss-und Mineralstoffwechsels pankreatischer Hunde, Beitr. z. chem. Phys. u. Path. **11**:224, 1908.

6. Kahn, M. and Kahn, M. H.: Lime Deficiency of Diabetes, Arch. Int. Med. **18**:212 (Aug.) 1916.

had coma or for other reasons must be regarded as poorly controlled have had extreme dental caries, and in at least one instance all the teeth had been lost by the time the patient had reached the age of 17. In a study of roentgenograms of 100 young persons with diabetes, 11 showed atrophy of bones.[7] It is only fair to add that this atrophy occurred among juvenile patients who had been treated for long periods without insulin. Atrophy of bones was observed in the years from 1924 to 1926 inclusive, and then disappeared. Dwarfism and roentgen evidence of transverse striae and delayed closure of epiphyses also occurred in this group.

ABNORMAL LOCAL DEPOSITS OF CALCIUM

Paradoxically, in the 2 patients with crushing of the vertebrae there existed extensive arteriosclerosis, with deposits of calcium in the peripheral arteries and the aorta. Such instances of extensive localized deposition of calcium are all too common in persons with diabetes. In the days before insulin was used, calcification of the arteries, demonstrable by roentgenogram or at autopsy, was the rule in patients with diabetes of more than five years' duration. Among 70 children with diabetes of seven or more years' duration, calcification of the arteries of the legs was demonstrated in 30 per cent. Morrison and Bogan [8] demonstrated that among 62 persons with diabetes of ten years' standing, 91 per cent had calcified peripheral arteries. Lehnherr [9] reported from the New England Deaconess Hospital that the aortas of patients with diabetes dying after the age of 50 on the average contained three times as much calcium as aortas of persons not having diabetes dying at a comparable age. The coronary vessels were found by Nathanson [10] to show calcification four times as often in persons having diabetes as in those not having it.

Localized deposits of calcium in the corium of the skin of patients with diabetes have occasionally been noted and will be the subject of a forthcoming paper by Drs. A. H. Davis and S. Warren of the pathologic laboratory of the New England Deaconess Hospital.

Cataracts in ocular lenses are known to contain in the advanced stages large amounts of calcium.[11] Among 294 young persons with

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7. White, P.: Diabetes in Childhood and Adolescence, Philadelphia, Lea & Febiger, 1932, p. 126.

8. Morrison, L. B., and Bogan, I. K.: Calcification of the Vessels in Diabetes; Roentgenographic Study of Legs and Feet, J. A. M. A. **92**:1424 (April 27) 1929.

9. Lehnherr, E. R.: Arteriosclerosis and Diabetes Mellitus, New England J. Med. **208**:1307 (June 22) 1933.

10. Nathanson, M. H.: Coronary Disease in One Hundred Autopsied Diabetics, Am. J. M. Sc. **183**:495 (April) 1932.

11. Updegraff, H.: Calcium, Phosphorus and Cholesterol in Cataractous vs. Apparently Normal Lenses from Human Eyes, Proc. Soc. Exper. Biol. & Med. **29**:964 (May) 1932.

diabetes, under 20 years of age, examined at the New England Deaconess Hospital by Drs. J. H. Waite and W. P. Beetham,[12] 3.8 per cent have shown progressive changes in the lens and an additional 1.1 per cent have shown less definite changes of this nature. Among 245 persons with diabetes over 30 years of age, examined at necropsy, Warren [13] found 25.3 per cent to have gallstones, as opposed to 13.5 per cent in 400 persons of similar ages not having diabetes. Pancreatic calculi have been discovered in 3 persons by roentgenogram and at autopsy in 3 additional cases. Wilder [14] reported 3 such cases among 58 autopsies on persons with diabetes. In their report of autopsies on 25 persons with pancreatic calculi, Ackman and Ross [15] stated that 10, or 40 per cent, had glycosuria. Morrison and Bogan [16] described pancreatic calculi in 8 cases in which 4 of the patients had diabetes.

FACTORS INFLUENCING CALCIUM AND PHOSPHORUS METABOLISM

Factors which might be operative in diabetes are: (1) age of the patient; (2) activity of the patient; (3) amount of lime salts in diet; (4) great excess in diet of calcium over phosphorus, and vice versa; (5) achlorhydria or hypochlorhydria and diminished or lacking pancreatic lipolytic ferment, two conditions frequently found in diabetic patients (either deficiency may be associated with diarrhea and this may prevent a proper absorption of calcium); (6) prolonged diarrhea from other causes; (7) prolonged acidosis; (8) excessive fat in the diet, particularly if unabsorbed (it is true that Mallon and her co-workers [17] found that in 2 normal subjects the amount of fat in the diet had no definite influence on the retention of calcium; their high fat diet, however, actually contained on the average only 105.6 Gm. of fat per day, and, furthermore, the studies made by these authors were of very short duration); and (9) deficient or excessive supply of vitamin D substances. An interesting suggestion is that possibly the hypercholesteremia so frequently observed in persons with

12. Waite, J. H., and Beetham, W. P.: Unpublished data.

13. Warren, S.: The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1930, p. 106.

14. Wilder, R. M.: Necropsy Findings in Diabetes, South. M. J. **19**:241 (April) 1926.

15. Ackman, F. D., and Ross, A.: Pancreatic Lithiasis, Surg., Gynec. & Obst. **55**:90 (July) 1932.

16. Morrison, L. B., and Bogan, I. K.: Pancreatic Calculi, New England J. Med. **199**:1129 (Dec. 6) 1928.

17. Mallon, M. G.; Jordan, R., and Johnson, M.: A Note on the Calcium Retention on a High and Low Fat Diet, J. Biol. Chem. **88**:163 (Aug.) 1930.

diabetes is associated with an increase in ergosterol, which, if activated, may increase the deposit of calcium in diabetic arteries or elsewhere.[18]

DAILY REQUIREMENT OF CALCIUM

Sherman's [19] figures place the desired amount of calcium in the daily diet for the average adult at 0.68 Gm., and for the growing child at 1.0 Gm. The desirable amount of phosphorus is stated as 1.32 Gm. a day. These figures were derived from metabolic studies on normal persons. To the average minimum intake found capable of preventing a negative calcium balance Sherman added 50 per cent to secure the figures cited. Naturally, therefore, it may be that with a great many persons these figures allow a very liberal margin of safety, thus explaining why instances of osteoporosis are not more common in those who have lived on a nonsupervised diet containing considerably less lime salts than the theoretical optimum amount.

CALCIUM IN DIABETIC DIETS

From a study of several representative diets given to patients at the New England Deaconess Hospital it was found that the "basic" diet (i. e., the diet exclusive of milk, cream and cheese) averages about 0.4 Gm. of calcium a day. It is therefore inadequate. However, by merely adding a glass (180 cc.) of milk and 120 cc. of 20 per cent cream or 15 Gm. of cheese and 150 cc. of 20 per cent cream, one can easily satisfy the calcium requirement. It is difficult to do this unless use is made of dairy products or eggs, since other foods have a relatively low calcium content. Sherman has shown, too, that calcium in vegetables is not as effectively absorbed or utilized as that in milk. Although Mallon and her associates [20] more recently demonstrated that fresh green lettuce is a satisfactory source of calcium, the quantities which must be ingested are large.

The amount of calcium in calcium-rich foods may be remembered easily if the following values are kept in mind. Approximately 0.1 Gm. of calcium is contained in each of the following foods: milk, 86 Gm. (about 3 oz.); cream (20 per cent), 108 Gm. (about 4 oz.); cheese, 11 Gm. (about ⅓ oz.); eggs, 3.

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18. Rabinowitch, I. M.: Observations on the Significance of the Cholesterol Content of the Blood Plasma in Diabetes Mellitus, Canad. M. A. J. **28**:162 (Feb.) 1933.

19. Sherman, H. C.: Phosphorus Requirement of Maintenance in Man, J. Biol. Chem. **41**:173, 1920; Calcium Requirement of Maintenance in Man, ibid. **44**:21, 1920; Chemistry of Food and Nutrition, New York, The Macmillan Company, 1932, chapts. xiii and xxiii.

20. Mallon, M. G.; Johnson, L. M., and Darby, C. R.: The Calcium Retention on a Diet Containing Leaf Lettuce, J. Nutrition **6**:303 (May) 1933.

An excellent plan is that, followed in the Indiana University Hospitals at Indianapolis [21] and in other institutions, of providing special columns on the diet sheet of diabetic patients for recording the amount of calcium and phosphorus given the patient, along with the figures for carbohydrate, protein and fat. If the calcium requirement is met, one need not be greatly concerned with the phosphorus content of the diet, since the two elements accompany each other in most foods.

COMMENT

Sufficient data have been presented to show that various types of abnormalities of deposition of calcium are found in diabetes mellitus. On the one hand, there are conditions of lack of calcium which are due, we believe, either (1) to lack of lime salts or vitamin D in the diet or to other causes operative as well in the person without diabetes or (2) to prolonged acidosis. There is little or no evidence in recent literature to suggest that in patients with well controlled diabetes there is any significant disorder of calcium metabolism attributable to the diabetes itself. Indeed, von Noorden [4] quotes with apparent agreement the statement of Gaethgens that "when there is no acidosis, the calcium metabolism of diabetic patients is the same as that of ordinary people." We have found the calcium and phosphorus content of the blood of patients with controlled diabetes invariably to be normal. It is significant in this connection that while Cammidge [22] found a low blood calcium in 44 per cent of his diabetic patients, Kylin [23] reported that his patients have values higher than normal. Wishnofsky [24] found, by studying dextrose tolerance curves, that calcium chloride given intravenously did not appear to influence the tolerance of patients with diabetes for dextrose.

On the other hand are the conditions, such as arteriosclerosis, cataracts and calculi of various sorts, in which calcium salts are deposited in excess locally. As yet no one has brought forward proof that these are to be regarded as disorders of calcium metabolism per se. These abnormalities of calcium deposition which are so often associated with serious clinical consequences seem therefore to depend on the duration and severity of the diabetes and to be controllable chiefly by its early, adequate and prolonged treatment.

21. Rudesill, C. L.: Personal communication.

22. Cammidge, P. J.: Retinitis in Diabetics, Proc. Roy. Soc. Med. (Sect. Ophth.) **23**:24 (Jan.) 1930.

23. Kylin, E.: Ueber den Kalkumsatz bei Diabetes mellitus, Acta med. Scandinav. **66**:197, 1927.

24. Wishnofsky, M.: Studies in Calcium and Carbohydrate Metabolism; Calcium and Glucose Tolerance in Diabetes Mellitus, J. Lab. & Clin. Med. **13**: 133 (Nov.) 1927.

In the present state of knowledge, treatment must provide adequate calcium and phosporus in the diet regardless of theoretical considerations that by so doing localized calcifications may be favored. We regard it essential to provide for all patients, particularly growing children, the optimum amount of lime salts in the daily diet. This should be supplemented, when indicated, by appropriate doses of cod liver oil, halibut liver oil or viosterol.

LIVER EXTRACT THERAPY IN CIRRHOSIS OF THE LIVER

RELATION OF LIVER DYSFUNCTION TO NONSTORAGE OF "ANTI-ANEMIC" SUBSTANCE IN PRODUCING A BLOOD PICTURE RESEMBLING PERNICIOUS ANEMIA IN A PATIENT SECRETING FREE HYDROCHLORIC ACID

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The following case is reported in the hope that it may possibly throw new light on a group of patients who have been described as having a blood picture resembling that of pernicious anemia, but who have the ability to secrete hydrochloric acid in their stomachs.

REPORT OF A CASE

History.—R. M., a white man, aged 58, was admitted to the University Hospital on Oct. 27, 1931, complaining chiefly of "pain in the abdomen." Three months previously, he first noted a dragging and generalized discomfort in the abdomen below the umbilicus. This sensation became progressively worse and after nine weeks nausea developed. The pain was not related to the intake of food. Although the patient did not go to bed because of the pain, it was necessary for him to stop working. One week before admission, he noted that his stools were black and watery; he thought that this was the result of medication which was given him for "enlargement of the liver." There had not been hematemesis, jaundice, chills or fever. His appetite was extremely poor, and he had lost about 10 pounds (4.5 Kg.) in weight in three months.

Physical Examination.—The patient showed evidence of recent loss of weight. The skin and the mucous membranes were pale. The teeth showed marked evidence of caries. The heart was of borderline size, regular in action, with a rate of 60 a minute; the blood pressure was 122 systolic and 80 diastolic. The abdomen was distended, and there was marked tenderness over the region just below the umbilicus, less evident in the epigastrium. The liver and spleen were not palpable. The veins of the abdominal wall were slightly distended, suggesting a compensatory collateral circulation.

Laboratory Observations.—The urine and stools showed no abnormalities. Gastric analysis following the injection of 1 mg. of histamine hydrochloride showed free acid in all specimens. The specimen following fasting contained 4 degrees of free acid; and at ten minute intervals the amounts of free acid found were: 15, 74, 87, 61 and 83 degrees. The red cell count was 2,590,000 per cubic milli-

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meter; the hemoglobin, 61 per cent (Sahli); the white cell count, 5,850; moderate poikilocytosis was present; 51 per cent of the red cells were larger than 7.5 microns, varying in size from 3.0 to 12.0 microns. Repeated roentgen and fluoroscopic examinations of the gastro-intestinal tract revealed only "fixation and tenderness over the appendix and cecum." The Kahn test was negative.

Course in Hospital.—Because of the pain in the lower part of the abdomen, loss of weight and anemia, an exploratory operation was performed on Nov. 19, 1931, by Dr. E. Potter. The stomach and duodenum were normal so far as could

Data in the Case Reported

Date	Red Blood Cells, Millions per C.Mm.	White Blood Cells, per C.Mm.	Hemoglobin, per Cent	Differential Count*	Reticulocytes, per Cent	Day of Treatment	Treatment
11/10/31	2.59	9,000	61	.....	...	..	
12/14/32	2.22	10,800	41	P. 71.0 E. 1.0 L.L. 12.0 S.L. 9.5 Mon. 6.5	8.7	..	
12/19/32	2.38	7,600	44	.....	...	..	Transfusion, 500 cc.
12/20/32	....	.....	51	.....	...	..	
12/22/32	....	.....	62	.....	...	..	Transfusion, 500 cc.
12/26/32	3.09	.....	57	.....	...	..	
12/29/32	3.16	11,700	55	.....	2.8	..	
12/30/32	2.68	11,100	48	.....	3.9	0	Intravenous liver extract, 20 cc.
12/31/32	....	.....	..	.....	5.2	1	
1/ 1/33	....	.....	..	.....	5.3	2	
1/ 2/33	....	.....	..	.....	7.9	3	
1/ 3/33	....	.....	..	.....	4.6	4	
1/ 4/33	....	.....	..	.....	5.1	5	
1/ 5/33	....	.....	..	.....	7.9	6	
1/ 6/33	2.75	9,700	49	.....	7.6	7	Intravenous liver extract, 20 cc.
1/ 7/33	....	.....	..	.....	8.5	8	
1/ 8/33	....	.....	..	.....	9.0	9	
1/ 9/33	....	....	..	.....	10.5	10	
1/10/33	....	.....	..	.....	10.5	11	
1/11/33	....	.....	..	.....	6.5	12	
1/12/33	....	.....	..	.....	6.1	13	
1/13/33	2.47	6,800	41	.....	5.2	14	Intravenous liver extract, 20 cc.
1/14/33	....	.....	..	.....	3.7	15	
1/15/33	....	.....	..	.....	4.6	16	
1/17/33	....	.....	..	.....	1.4	18	
1/19/33	2.06	7,750	44	.....	...	20	
2/11/33	3.89	12,100	53	.....	...	43	Intravenous liver extract, 20 cc.
3/ 3/33	3.99	8,800	64	.....	...	63	

* P. indicates polymorphonuclears; E., eosinophils; L.L, large lymphocytes; S.L., small lymphocytes; Mon., monocytes.

be determined by palpation. The gallbladder was small and contained no stones. The liver showed a moderate degree of cirrhosis without much enlargement. The appendix was fastened by adhesions and appeared to be the site of previous inflammation. It was removed in the routine manner.

The patient felt comparatively well for a few weeks following the operation; then the pain reappeared and became progressively more troublesome. It was dragging, dull and constant and had a tendency to become localized in the lower part of the abdomen. One month previous to his second admission, Dec. 19, 1932, he became aware of increased weakness and shortness of breath, coldness of the lower extremities and numbness and tingling, more marked in the feet than in the hands. His appetite again became extremely poor and the nausea returned, but the patient did not vomit. There was a loss of 20 pounds (9 Kg.) in weight in two months. The data from the physical examination were practically the

same as on the previous visit. Roentgenograms at this time suggested an obstructing carcinoma in the proximal transverse colon.

A second laparotomy was performed by Dr. Potter on Dec. 23, 1932. A rather marked generalized fibrinopurulent peritonitis was found. All the organs examined, except the liver, were essentially normal. There was no evidence of carcinoma of the colon.

Six days after the operation, the patient was admitted to the Simpson Memorial Institute. The blood count at this time was somewhat elevated, owing to two blood transfusions. The red cell count was 3,160,000; the hemoglobin, 55 per cent (Sahli); and the white blood cell count, 11,700. Following treatment with purified liver extract given intravenously, as suggested by Dr. Raphael Isaacs, the reticulocytes, on the tenth and eleventh days, reached a peak of 10.5 per cent. Although the response was somewhat delayed, this is the calculated maximum response for a patient with true pernicious anemia.[1] Thereafter he received similar treatments (a total of four) at weekly intervals, and when last observed, sixty-three days after the initial treatment, his condition was distinctly improved. The red cell count was 3,990,000; the hemoglobin, 64 per cent (Sahli); and the white cell count, 12,100. Details of the blood studies are given in the table.

COMMENT

Castle [2] has proposed that pernicious anemia may be the result of the absence of an extrinsic factor (possibly vitamin B_2) or the absence of an intrinsic factor in gastric juice. Sturgis and Isaacs [3] have shown that stomach tissue alone develops the active principle; Minot and Murphy,[4] that the active principle is present in liver; and Richter, Ivy, and Kim [5] have gone a step further and demonstrated that the active principle is stored in the liver.

From these studies, it would appear that the syndrome of pernicious anemia might possibly result from or be produced in three ways: (1) by the absence of the proper food factors; (2) by the absence of the activating secretion in the stomach; (3) by the failure to absorb the product necessary for the maturation of the red blood cells. To these is added a fourth possibility. With the destruction of the liver, the excess of the product essential for the growth of the red cells, produced during digestion, may be lost, owing to the inability of the damaged hepatic tissue to

1. Bethell, F. H., and Goldhamer, S. M.: Standards for Maximum Reticulocyte Values Following Ventriculin and Intravenous Liver Extract Therapy in Pernicous Anemia, Am. J. M. Sc. **186**:480 (Oct.) 1933.

2. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, Am. J. M. Sc. **178**:748 (Dec.) 1929. Strauss, M. B., and Castle, W. B.: The Nature of the Extrinsic Factor of the Deficiency State in Pernicious Anemia and in Related Macrocytic Anemias, New England J. Med. **207**:55 (July 14) 1932.

3. Sturgis, C. C., and Isaacs, R.: Desiccated Stomach in the Treatment of Pernicious Anemia, J. A. M. A. **93**:747 (Sept. 7) 1929.

4. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**:470 (Aug. 14) 1926.

5. Richter, O., Ivy, A. C., and Kim, M. S.: Action of Human "Pernicious Anemia Liver Extract," Proc. Soc. Exper. Biol. & Med. **29**:1093 (June) 1932.

store it, as suggested by the case of cirrhosis of the liver herein presented. It is conceivable that sufficient hematopoietic stimulating material may be manufactured and absorbed to maintain the normal red cell count, but that it cannot be stored for usage during the interval between meals. If this supposition is correct, the red cell count may not be maintained at a normal level, owing to a deficient storage capacity of the liver, but may drop to a low level of from 2,500,000 to 3,000,000 cells, and remain there. With this idea in mind, it would perhaps have been better to give treatments at more frequent intervals in this unusual condition.

The hypothesis of failure or decreased storage would enable one to account for the various etiologic factors which are known to give the picture of pernicious anemia, whether free acid is present or not in the gastric juice. If the stomach is involved, free acid as a rule is not secreted, but if the disturbance is only in absorption [6] or storage, free acid may possibly be formed. This factor of the disturbance of storage may account for the blood pictures resembling that of pernicious anemia which are seen in the so-called pernicious anemia of pregnancy and other diseases accompanied by macrocytosis.

Cases of cirrhosis of the liver with anemia, a macrocytosis and a color index of 1 or more have been described by Holler and Kudelka,[7] Cheney and Niemand,[8] Masina [9] and others; the mechanism described in this paper is suggested as the possible cause for the specific blood picture.

SUMMARY

1. A case of cirrhosis of the liver is reported in which free hydrochloric acid was present in the gastric contents and in which the blood picture simulated that of true pernicious anemia. The response to intravenous liver therapy was similar to that observed in patients with true pernicious anemia.

2. In addition to factors of defective gastric secretion, defective intake of food and inadequate absorption, a fourth factor in the production of a blood picture resembling that of pernicious anemia is suggested to be the interference of the storage of the material necessary for the maturation of the red blood cells.

6. Castle, W. B., Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, Am. J. M. Sc. **182**:741 (Dec.) 1931.

7. Holler, G., and Kudelka, O.: Resultate von Bestimmungen des Erythrozytendurchmessers beim Menschen unter physiologischen und pathologischen Verhältnissen, Folia haemat. **35**:197 (Nov.) 1928.

8. Cheney, G., and Niemand, F.: The Treatment of Secondary Anemia with "Secondary Anemia Liver Extract" and Iron, Am. J. M. Sc. **184**:314 (Sept.) 1932.

9. Masina, N.: Das Blutbild bei Leberzirrhose mit besonderer Berücksichtigung der Monozytengranulation, Folia haemat. **46**:335 (March) 1932.

PHYSIOLOGY OF VITAMINS

XXIII. THE EFFECT OF LACK OF THE VITAMIN B COMPLEX ON THE SECRETION OF GASTRIC JUICE IN DOGS WITH GASTRIC POUCHES

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A study of the effect of lack of the vitamin B complex on gastric secretion is of interest for several reasons. The first is based on analogy and is concerned with that vicious circle of pernicious anemia, gastric achylia and subacute combined sclerosis. This group of symptoms has been termed "combined system disease." The relationships of the elements of this syndrome are fascinating in their implications.

It is well recognized that practically all cases of pernicious anemia are characterized by gastric achylia. In support of this view, observations of Minot and Murphy [1] and others indicating that pernicious anemia may well be classified as a deficiency disease, and the findings of Castle [2] that impaired gastric function plays an important rôle, may be cited. According to some investigators in this field (Hurst and Bell,[3] Collier [4] and Vanderhoof [5]), there is an almost invariable asso-

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Because the diets used in this study were markedly but not absolutely deficient in either vitamin B (B_1) or G (B_2), we use the expression "lack of vitamin B complex."

This paper is a report of some of the data contained in the dissertation presented by Alfred Gilman in partial fulfilment of the requirements for the degree of Doctor of Philosophy, Yale University, 1931.

1. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia, J. A. M. A. **89**:759 (Sept. 3) 1927.

2. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, Am. J. M. Sc. **178**:748, 1929.

3. Hurst, A. F., and Bell, J. R.: The Pathogenesis of Subacute Combined Degeneration of the Spinal Cord, with Special Reference to Its Connection with Addison's (Pernicious) Anemia, Achlorhydria and Intestinal Infection, Brain **45**: 266, 1922.

4. Collier, J.: Intrinsic Diseases of the Spinal Cord, in Christian, H. A., and Mackenzie, James: Oxford Medicine, New York, Oxford University Press, 1921, vol. 6, pp. 327 and 356.

5. Vanderhoof, Douglas: The Etiologic Relation of Achylia Gastrica to Combined Sclerosis of the Spinal Cord, Arch. Int. Med. **32**:958 (Dec.) 1923.

ciation of achylia gastrica with combined sclerosis of the spinal cord. Furthermore, in many cases there may be observed lesions of the spinal cord associated with gastric achylia and the absence of an associated anemia as a complicating condition. This has led Hurst and Bell [3] and Vanderhoof [5] to believe that the fundamental cause of spinal sclerosis may be achlorhydria. Treatment of such sclerosis with oral administration of hydrochloric acid has been tried and believed to prove efficacious.

Pathologic findings on dogs that have succumbed to lack of the vitamin B complex were interpreted by Gildea, Kattwinkel and Castle [6] as indicating degeneration of the spinal cord. The lesions were believed to bear a marked similarity to those associated with achylia gastrica and pernicious anemia. Zimmerman and Burack,[7] however, failed to confirm these observations. In the work just cited there is a hint that a possible explanation of the neurologic findings associated with a deficiency of the vitamin B complex may be found in a gastric disturbance.

Another reason for the interest in the gastric secretion during lack of the B complex lies in the existence of other gastric symptoms observed during the course of the deficiency. Karr [8] and Cowgill [9] demonstrated that dogs lose their normal urge to eat when deprived of this dietary factor. According to Rose, Stucky and Cowgill,[10] gastric motility is usually markedly depressed during the advanced stages of the deficiency. Observations of the secretory activity of the stomach in animals subsisting on diets adequate except for the vitamin B complex would seem, therefore, to be a logical sequel to these studies.

Perusal of the literature reveals that there have been only a few investigations of the influence on gastric secretion of a dietary regimen deficient in the B complex. Danysz and Koskowski [11] conducted studies on pigeons which (*a*) received a normal diet, (*b*) were starved, (*c*) received a diet of polished rice, and (*d*) received polished rice plus a

6. Gildea, E. F.; Kattwinkel, E. E., and Castle, W. B.: Experimental Combined System Disease, New England J. Med. **202**:523, 1930.

7. Zimmerman, H. M., and Burack, Ethel: Lesions of the Nervous System Resulting from Deficiency of the Vitamin B Complex, Arch. Path. **13**:207 (Feb.) 1932.

8. Karr, W. G.: Some Effects of Water-Soluble Vitamin upon Nutrition, J. Biol. Chem. **44**:255, 1920.

9. Cowgill, G. R.: A Contribution to the Study of the Relation Between Vitamin-B and the Nutrition of the Dog, Am. J. Physiol. **57**:420, 1921.

10. Rose, W. B.; Stucky, C. J., and Cowgill, G. R.: Studies in the Physiology of Vitamins: XIII. The Relation of Gastric Motility to Anhydremia in Vitamin B-Deficient Dogs, Am. J. Physiol. **92**:83, 1930.

11. Danysz, Michel, and Koskowski, W.: Etude de quelques fonctions digestives chez les pigeons normaux, nourris au riz poli et en inanition, Compt. rend. Acad. d. sc. **175**:54, 1922.

daily injection of 0.1 mg. of histamine. The integrity of the gastric glands was tested by chemical examination of the gastric secretion subsequent to stimulation with histamine. The responses yielded in groups *a*, *b* and *d* were practically normal. Group *c*, however, exhibited a marked decrease in both volume and acidity of secretion combined with an almost complete loss of peptic activity.

The investigations of Farnum [12] were conducted on dogs possessing Pavlov gastric pouches. The diet offered these animals is not reported. However, it was supposedly rendered free from vitamin B by autoclaving in an alkaline medium. The experimental animals showed a progressively decreasing function of the gastric glands as evidenced by diminished volume and acidity of the secretion. Protocols of the intake of food were not given, but it is highly probable that the decrease in gastric function exhibited by these animals was chiefly a reflection of the anorexia which is characteristic of such a dietary deficiency. It was also reported that the animals receiving the faulty diet were more refractory in their response to histamine, larger doses of this drug being required to produce an effect equal to that characteristic of the animal on a normal dietary regimen. The response of the gastric glands to gastrin was reported as being normal at all times. This might be interpreted as failing to confirm Ivy's [13] idea that gastrin is histamine.

The experiments of Gildea, Kattwinkel and Castle [6] were less quantitative. The dogs were divided into three groups and placed on diets believed to be deficient primarily in (*a*) the vitamin B complex, (*b*) antineuritic vitamin B (B_1) and (*c*) vitamin G (B_2). Gastric function was determined by the response to injections of histamine. Dogs with gastric pouches were not used; instead, a single sample of gastric juice was aspirated from the stomach thirty minutes after the gastric stimulant had been injected. These investigators were able to demonstrate the presence of free hydrochloric acid in the secretion of every animal, even when the symptoms of deficiency in vitamins were severe. The juice also had a normal concentration of pepsin. Repeated injections of histamine in no way alleviated or postponed the symptoms characteristic of a B avitaminosis.

As can be seen from these brief summaries of previous investigations, a wide difference of opinion exists as to the ability of the gastric glands to function during a dietary regimen characterized by a deficiency of both the vitamin B complex and its separate B (B_1) and G (B_2) components. In the experiments about to be described, the technic was fundamentally the same as in that used by Gildea, Kattwinkel and

12. Farnum, M. B.: Gastric Secretion in Experimental Beriberi in the Dog, Arch. Int. Med. **37**:212 (Feb.) 1926.

13. Ivy, I. C.: Personal communication to the authors.

Castle, who used dogs as the experimental subjects. The animals were provided with gastric pouches of the Pavlov and the Heidenhain type, respectively. Histamine was used as the gastric stimulant.

I. THE EFFECT OF A DIET DEFICIENT IN ANTINEURITIC VITAMIN B ON THE SECRETION AND CHEMICAL COMPOSITION OF GASTRIC JUICE

Diet Used.—In the first series of experiments the dogs were fed the casein III diet, details of which have been described elsewhere (Cowgill[14]). This ration has been used repeatedly in vitamin studies on dogs and shown to be markedly deficient in the antineuritic B_1 component of the vitamin B complex; in all probability, judging from the observations of Cowgill, Stucky and Rose,[15] it is very low in its content of the heat-stable G (B_2) factor. In view of the facts (*a*) that a much longer time is required to deplete the tissues of vitamin G (B_2) than is the case for the B (B_1) substance (Bing and Mendel,[16] Sherman and Sandels[17] and Graham and Griffiths[18]) and (*b*) that subsistence on the casein III diet results in the development of nerve lesions that are characteristic and quite different from those due to lack of vitamin G (B_2) alone (Zimmerman and Burack[7] and Zimmerman[19]), we believe that the phenomena observed in the animals of this series may be definitely attributed to lack of vitamin B (B_1).

Prior to the period of subsistence on this diet alone each animal received a supplement of vitavose[20] (1 Gm. per kilogram a day) designed to supply the needed B vitamins. The diet so supplemented is complete in every known respect; dogs subjected to such a dietary regimen have maintained an excellent nutritive condition over a period of three years.[21]

The normal response of the gastric glands of the experimental animals subsisting on this complete ration was first determined. The administration of vitavose was then discontinued, and tests of gastric

14. Cowgill, G. R.: Physiology of Vitamins: II. Parenteral Administration of Vitamin-B—Mammalian Experiments, Am. J. Physiol. **66**:164, 1923.

15. Cowgill, G. R.; Stucky, C. J., and Rose, W. B.: The Physiology of Vitamins: V. Cutaneous Manifestations Related to a Deficiency of the Vitamin B Complex, Arch. Path. **7**:197 (Feb.) 1929.

16. Bing, F. C., and Mendel, L. B.: The Vitamin B and the Vitamin G Requirements of the Albino Mouse, J. Nutrition **2**:49, 1929.

17. Sherman, H. C., and Sandels, M. R.: Further Experimental Differentiation of Vitamins B and G, J. Nutrition **3**:395, 1931.

18. Graham, C. E., and Griffiths, W. H.: Vitamins B_1 and B_2 in Tissues of Normal and Experimental Rats, Proc. Soc. Exper. Biol. & Med. **29**:695, 1932.

19. Zimmerman, H. M.: Personal communication to the authors.

20. A soluble vitamin B preparation made from wheat germ.

21. Drabkin, D. L.: Personal communication to the authors.

function were made at intervals until the symptoms characteristic of a lack of vitamin B developed in the animals. The ration was then again supplemented with the necessary dietary essential and the gastric secretory power determined during the animal's recovery period.

Gastric Function Tests.—The most physiologic approach to the problem under investigation would be the use, as a gastric stimulant, of a definite food of a constant composition and the determination of the subject's response to this normal stimulus. However, one of the earliest and most constant symptoms of a lack of vitamin B is anorexia. Therefore, it is impossible to use a voluntary consumption of food as a stimulus in this study. It is also difficult to devise a liquid test meal adequate in all respects except for the vitamin B complex which is suitable for administration by stomach tube and capable of exciting a generous flow of juice. Subcutaneous injection of histamine, however, can be used as a test for gastric function with great facility. It has been shown that histamine does not promote the secretion of pepsin, although it does stimulate the flow of water and hydrochloric acid (Gilman and Cowgill [22] and Vineberg and Babkin [23]). Therefore, when using this drug one is observing the basal and unstimulated secretion of enzymes. Even such an observation is significant. If the basal activity of the chief cells is unaffected by the deficiency in vitamin B, one might consider these cells capable of normal function. It is, of course, possible to take the view that the use of histamine is contraindicated on the ground that it is so powerful a stimulus—that observation of the production of an acid gastric juice in response to injection of histamine cannot be taken as indicating that the glands would show a similar response to the weaker, but more physiologic, stimulus such as results from the consumption of food.

Samples of gastric secretion were analyzed for pepsin by the Gilman and Cowgill [24] method, for free and combined hydrochloric acid by titration with fiftieth-normal sodium hydroxide using Topfer's reagent and phenolphthalein, respectively, as indicators, and for total chlorides by the method of Van Slyke (1923). Neutral chloride was estimated from the difference between acid and total chloride.

In experiments of the nature described it is important to determine the constancy of the response of the gastric glands to the same stimulus. This was accomplished by repeated tests with the same dose

22. Gilman, A., and Cowgill, G. R.: The Effect of Histamine upon the Secretion of Gastric Pepsin, Am. J. Physiol. **97**:124, 1931.

23. Vineberg, A. M., and Babkin, B. P.: Histamine and Pilocarpin in Relation to Gastric Secretion, Am. J. Physiol. **97**:69, 1931.

24. Gilman, A., and Cowgill, G. R.: The Determination of Peptic Activity: An Examination and Application of the Gates Method of Proteolytic Enzyme Titration, J. Biol. Chem. **88**:743, 1930.

of histamine on each animal during the preliminary period of subsistence on the adequate diet. These observations were made at least three weeks subsequent to the pouch operation, and after the animal had become completely accustomed to the routine of the experiment. Only after a sufficient number of these tests had been performed, so that the characteristic response of the completely nourished animal was established and easily recognized, was the daily supplementation of the diet with vitavose discontinued.

Results.—Since the results yielded by the different animals varied appreciably, pertinent data obtained from each dog are given. In order to show the kind of data secured in each experiment, an illustrative protocol (table 1) is presented.

TABLE 1.—*Protocol of Experiment with Dog Petunia, May 8, 1930* *

Time, Min.	Rate of Secretion, Cc. per Hour	Concentration of Chlorine			Pepsin		Mucus‡
		Acid, Milli-equivalents	Total, Milli-equivalents	Neutral, Milli-equivalents	Concentration,† Units per Cc.	Total Output, Units per Hour	
30	6.0	124.0	158.0	34.0	17,520	105,120	3
		3 Mg. of Histamine Chloride Injected Subcutaneously					
15	21.2	135.2	156.0	20.8	11,040	242,000	2
30	43.2	158.0	168.8	10.8	3,666	158,400	1
45	45.2	159.2	168.0	9.8	1,660	48,180	0
60	16.0	157.2	168.8	11.6	5,080	81,280	1
75	2.6	141.0	159.0	18.0	16,000	41,600	1

* The dog was subsisting on an adequate diet and was in excellent condition.
† One per cent solution of a 1:10,000 dilution of commercial pepsin is taken as equal to 1,000 units, as described by Gilman and Cowgill.[24]
‡ The amount present was estimated by the naked eye, and the results were expressed in terms of a scale of from zero to 3.

DOG "PETUNIA".—*Pavlov Pouch.*—This animal possessed a large pouch and thus produced a large volume of secretion. Observations were made over a preliminary period of about two months, during which time the volume and acidity of the gastric juice secreted in response to a constant dose of histamine varied but slightly. A protocol representative of one of these experiments is given in table 1.

The data presented in table 2 indicate roughly the constancy of the secretion so far as the volume of juice elaborated is concerned. The recorded rate of secretion is the maximum observed, occurring almost without exception forty-five minutes subsequent to the administration of the histamine. The rate of secretion in response to a given dose of histamine showed no appreciable change over a period of two months.

On July 15, the vitavose was removed from the diet and similar observations continued. On the eighteenth day of subsistence on the diet deficient in vitamin B (protocol, August 1) the maximum rate of secretion had fallen to 20.4 cc. per hour. On the twenty-first day the animal exhibited the characteristic anorexia. On the twenty-third and thirty-second days the maximum rates observed were 25.6 and 17.2 cc. per hour, respectively. The chemical composition of these samples was normal with respect to the variables under observation.

On the thirty-seventh day (August 20) a subcutaneous injection of histamine failed to produce gastric secretion. This experiment is of such interest that it is worth while to summarize it in detail. For thirty minutes the basal secretion of the stomach during fasting was collected. During that time the gastric glands produced only a very few drops of a thick viscous material. The animal was then given an injection of the usual dose of histamine. During the thirty minutes subsequent to this injection, the gastric secretion remained unchanged. At this point a second administration of histamine was superimposed on the first, with no effect on the gastric secretion. In order to make certain of the efficacy of the histamine employed, a fresh solution of the drug was made and injected in the dosage previously used. The dog was observed for another hour, during which time there was no secretion of a fluid gastric juice; only a fraction of a cubic centimeter of thick viscous product was collected. On analysis this material proved to be neutral in reaction. However, on extraction with acid it was demonstrated to possess an appreciable proteolytic activity.

No therapy was given the animal at this time, because it was considered desirable to repeat the foregoing experiment. On the following day (August 21), the animal was again subjected to the same experimental procedure, with identical

TABLE 2.—*Constancy in the Response of Dog Petunia to Injection of the Same Dose of Histamine Over a Period of About Two Months*

Date	Maximum Rate of Secretion, Cc. per Hour
May 8	45.0
May 10	44.8
May 13	46.0
May 15	37.2
May 19	45.6
May 21	42.4
July 2	39.0
July 15	40.4

results. After this trial the dog was given 50 Gm. of vitavose. A partial restoration of appetite was observed. Twenty-four hours after the administration of the vitamin the gastric secretory activity was again tested. The pouch, which during the previous few days had not contained any fluid, was partially filled with an acid juice. Stimulation with histamine produced a fairly generous flow of fluid, the maximum rate of secretion being 16.4 cc. per hour. Vitamin was again administered, and twenty-four hours later the rate of secretion had increased to 28.4 cc. per hour. The proteolytic activity of this secretion was within normal limits; however, the concentration of chloride was slightly lower than that usually observed.

A discussion of these results will be reserved until the data representative of the other experimental subjects have been presented. The fact to be kept in mind at this point, however, is that in the experiment just described, the dog at no time showed any of the symptoms of advanced deficiency in vitamin B, such as the neuromuscular manifestations.

DOG "BROWNIE".—*Pavlov Pouch.*—This dog, when tested from time to time, showed a fairly characteristic response to histamine. Four observations made on the animal, subsisting on the adequate diet, gave maximum rates of secretion of 22.4, 26.8, 24.4 and 26.4 cc. per hour. On the twenty-fourth day of the deficiency regimen the observed rate of secretion was 24.4 cc. per hour. The rate of secretion was still unaffected on the fiftieth day. The significantly low rate of 18.8 cc. per hour was exhibited on the fifty-seventh day. Symptoms of advanced vitamin

deficiency appeared on the seventy-seventh day. These were not severe, being confined to the hindlegs. The response to histamine at this time was definitely reduced, the maximum rate of secretion being only 10 cc. per hour. Furthermore, the period during which the stimulus was effective was shorter than that usually observed. The chemical composition of the gastric juice secreted under these conditions was not abnormal. The acidity and total chloride values were slightly low but not significantly so. The samples were just as rich, if not richer, in pepsin than those previously observed.

Vitamin therapy brought about a rapid disappearance of the nervous symptoms. The response of the gastric glands to histamine was also greatly changed. Twenty-four hours after the administration of vitamin the volume rate of flow of the gastric juice had increased to 18.8 cc. per hour. After seventy-two hours it had reached its normal value (30 cc. per hour). This dog was observed for more than a year subsequent to the completion of the experiment just described, during which period it subsisted on an adequate diet. During this time the rate of secretion was always quite constant and characteristic, the maximum averaging around 28 cc. per hour.

Dog "Bozo."—*Pavlov Pouch.*—Four preliminary observations on this animal yielded the characteristic normal rates of secretion in response to a constant stimulus with histamine of 17.2, 13.6, 13.2 and 13.5 cc. per hour. The dog was then placed on the diet deficient in vitamin B and exhibited anorexia after a period of only thirteen days. Other observations made in our laboratory suggest that this animal may have had a poorer utilization of ingested vitamin or else a greater loss of this dietary factor through excretory channels. On the thirty-third day of the deficiency regimen the rate of secretion had fallen to 6.8 cc. per hour. On the fortieth day very severe and typical symptoms of deficiency in vitamin B (B_1) developed. The rate of secretion at this time was 6.4 cc. per hour. Vitamin B therapy was followed within forty-eight hours by a maximum gastric response to histamine of 12.8 cc. per hour, which was very close to the previously observed normal value. The acid and pepsin contents of this juice were normal.

Dog "Dolores."—Heidenhain Pouch.—The results obtained from this animal may be summarized briefly. This dog, with few exceptions, gave a constant and characteristic response to histamine. The picture exhibited during subsistence on the diet deficient in vitamin B was also classic, anorexia appearing on the twelfth day and definite neuritic symptoms on the seventy-fourth day. However, even coincident with the onset of the neuromuscular manifestations, the gastric secretion remained unchanged with respect to both the volume of juice secreted and its contents of acid and pepsin.

Comment.—The results summarized are varied. In three of the four dogs there was definite evidence of a diminished response of the gastric glands to stimulation with histamine during the state of deficiency in vitamin B. If the lack of antineuritic vitamin is the etiologic agent causing this altered gastric response, how can one explain the fact that the animal Petunia, the secretion of which was most markedly affected, showed no symptoms of a deficiency of vitamin B other than anorexia? On the other hand, Dolores, which exhibited advanced symptoms of neuritis, gave no evidence of a diminished gastric activity. Yet it is strongly indicated that the lack of vitamin is the essential remote, if not immediate, cause of the diminished secretion, because as a result of administration of the vitamin the function of the gastric

gland was rapidly restored to normal in the three animals which exhibited this disturbance. It is difficult to reconcile these facts. In view of the observations of Rose, Stucky and Cowgill,[10] published since these experiments were performed, that a variable degree of anhydremia develops in deficiency of vitamin B, one might believe that the differences here noted are reflections of such a condition. The protocols of all the experiments were therefore examined from this point of view. The numerous data, omitted owing to lack of space, indicate clearly that one cannot attribute the changes in gastric response exhibited by these dogs to an accompanying anhydremia.

The fact that the three dogs possessing Pavlov pouches evidenced a diminished secretion, whereas the animal possessing a Heidenhain pouch remained normal so far as the gastric response is concerned, seems to be significant. The essential difference between these two types of pouches is that in the former the vagal nerve connections are intact, whereas in the latter the pouch has lost its primary vagal communication. However, one is at a loss to explain the observed results from such a consideration. In deficiency of vitamin B, the symptoms observed are characteristic of a hyperactivity rather than a hypo-activity of the nerves. A hypersensitivity of the vagus should lead to an increased rather than a decreased gastric secretion (Babkin [25]). In these studies, however, all the dogs with Pavlov pouches exhibited a diminished function of the gastric glands.

There remained as a possible explanation of these results the fact that the experimental diet was deficient in both the B (B_1) and G (B_2) components of the vitamin B complex. The casein III diet which was fed to these dogs is practically devoid of vitamin B. It is true that the commercial casein used in its preparation contains a slight amount of vitamin G (B_2). Could it be possible that the gastric symptoms observed were manifestations of a varying degree of deficiency of the last-named component of the vitamin B complex? Experiments were therefore undertaken to test this hypothesis.

II. THE EFFECT OF SUBSISTENCE OF DOGS WITH GASTRIC POUCHES ON THE GOLDBERGER DIET 195 ON THE SECRETION AND CHEMICAL COMPOSITION OF GASTRIC JUICE

At the time these experiments were undertaken no one had successfully fed dogs over long periods on purely artificial diets adequate except with respect to vitamin G (B_2). The experience of one of us (G. R. C.) had indicated that in all probability this constituted a separate problem, and until it had been investigated with success, it seemed unwise to begin such an experiment with dogs with gastric pouches.

25. Babkin, B. P.: Vagal and Sympathetic Control of Gastric Secretory Functions, Tr. Am. Gastro-Enterol. A., to be published.

Goldberger and his associates,[26] however, fed dogs certain food mixtures and observed the appearance of the canine disease called black tongue, which was believed to be the analog of pellagra in man and to be due chiefly, if not solely, to lack of vitamin G (B_2). It is quite likely, in view of more recent developments,[27] that these ideas of Goldberger and his co-workers require some modification. Since subsistence of dogs on the Goldberger 195 diet results in quite prompt production of a characteristic syndrome, it was believed that trials of this diet with our dogs with gastric pouches might enable us to determine the rôle, if any, of deficiency in vitamin G in bringing about changes in gastric response.

Experimental Data.—The experimental procedure in these studies was the same as that described in part I, with the exception of the diet employed. After the characteristic response of the dog subsisting on an adequate diet had been determined, the animal was given the Goldberger diet 195, and the observations were continued until manifestations of black tongue appeared, and therapy had been instituted. Four dogs were studied. Two of these animals had already been observed in the previous study. Thus dog Dolores, having shown no signs of gastric disturbance when subsisting on casein III ration, was realimented and then given the Goldberger diet. Dog Bozo, having shown a lessened gastric secretion when on the casein III diet, after realimentation was similarly given the black tongue-producing ration. In addition, two other dogs were included. In this study, therefore, there were two dogs with Pavlov pouches and two animals with Heidenhain pouches.

Results.—In view of the variations noted, it will facilitate proper understanding of the results if pertinent data for each animal are presented separately.

Dog "Dolores."—*Heidenhain Pouch.*—This animal, while subsisting on the Goldberger diet, continued to secrete gastric juice in a normal fashion. After fourteen days on this ration a cage sore began to develop on the right hindleg over the protuberance of the proximal extremity of the femur. Before the completion of the experiment this sore had grown to tremendous proportions. In addition, symmetrically placed lesions of the skin appeared on each side of the head at the angle of the mandible and over the superciliary arches of the frontal bone. Lesions also appeared over the thorax, extending from the fifth to the seventh intercostal spaces. These were also symmetrically placed. Additional lesions were also noted over each clavicle.

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26. Goldberger, J., and Wheeler, G. A.: Experimental Black Tongue of Dogs and Its Relation to Pellagra, Pub. Health Rep. **43**:172, 1928. Goldberger, J.; Wheeler, G. A.; Lillie, R. D., and Rogers, L. M.: A Further Study of Experimental Black Tongue, with Special Reference to the Black Tongue Preventive in Yeast, ibid. **43**:657 and 663, 1928.

27. For recent reviews relating to this topic see Sure, B.: The Present Status of Vitamin B_2 (G), J. A. M. A. **99**:26 (July 2) 1932, and Underhill, F. P.: Clinical Aspects of Vitamin G Deficiency, ibid. **99**:120 (July 9) 1932.

The dog's appetite over the first sixty days of the experiment was good, during which time she maintained her body weight. From the sixtieth to the seventy-eighth day the intake of food was erratic; the animal became rapidly weaker, and on the seventy-eighth day she refused all of the food offered. At this time the dog was most apathetic. A test of the stomach, however, revealed normal glandular response to histamine. Daily administrations of yeast were made in an attempt to save the dog's life. In spite of this therapy the animal died eighty-two days after the beginning of the experiment. It is interesting that at no time did this animal show any of the oral or intestinal lesions that have been described by Goldberger and attributed to deficiency in vitamin G (B_2).

Dog "Roberta."—*Pavlov Pouch.*—This dog had been observed over a period of eight months preceding the experiment to be described. During this period repeated tests showed her gastric secretory response to have been remarkably constant. The septum separating the gastric pouch from the main stomach was perforated. However, careful drainage permitted the quantitative evacuation of the contents of the pouch without contamination by material from the main stomach. The dog consumed the Goldberger diet ravenously and maintained a constant body weight. This continued for eighty-one days, during which time the secretion remained perfectly normal. On the eighty-first day the animal refused all the food offered. A test of gastric function was made on the eighty-sixth day. At this time the animal was regurgitating so much of the intestinal secretions that it was impossible to collect pure gastric juice because of contamination of the contents of the pouch through the perforated septum. However, a large volume of fluid containing free acid was obtained. The presence of free acid is significant because of the fact that the juice was contaminated with bile and doubtless alkaline pancreatic fluid. That one was able to obtain a sample of acid gastric secretion under such conditions indicates that the parietal cells were functioning in a capable manner. On the eighty-ninth day the characteristic lesions of the mouth developed, accompanied by profuse salivation, as described by Goldberger and his associates [26] and Underhill and Mendel.[28] A test of the gastric function made at this time revealed normal secretion. Fifty grams of whole yeast was administered by stomach tube. Twenty-four hours later no relief of the symptoms was evident. An additional 50 Gm. of whole yeast was given. On the following day the dog was found dead. Autopsy revealed diffuse hemorrhage in both lungs. It is believed that the primary cause of death of this animal was pneumonia, the development of which was probably facilitated by prolonged subsistence on the faulty diet.

One interesting lesion exhibited by this animal, which developed after sixty days of subsistence on the deficient diet, was loss of hair from the tip of the tail. The influence of the injection of histamine on this lesion was striking. When it first developed, the administration of histamine so affected the permeability of the capillaries at the tip of the tail that transudate would cross the capillary wall, as evidenced by the appearance of droplets on the exposed skin. The volume of this transudate was sufficiently great to cause a steady dripping from the end of the tail. After two weeks, however, these caudal capillaries apparently had lost their function to such an extent that the administration of histamine failed to produce any increased permeability, as evidenced by the fact that the exposed tissue remained perfectly dry.

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28. Underhill, F. P., and Mendel, L. B.: A Dietary Deficiency Canine Disease: Further Experiments on the Diseased Condition in Dogs Described as Pellagra-Like by Chittenden and Underhill and Possibly Related to So-Called Black Tongue, Am. J. Physiol. **83**:589, 1928.

Dog "Bozo."—*Pavlov Pouch.*—It will be recalled that this dog showed a definitely diminished gastric secretion when subsisting on the diet deficient in vitamin B (B_1). In the present experiment there was no evidence of abnormality in this respect on the hundredth day of subsistence on the Goldberger diet. The experiment was terminated on the hundred and twelfth day.

Dog "Ethyl."—*Heidenhain Pouch.*—This animal became a coprophagist. Since the results obtained from the dogs already cited had been negative, no effort was made to keep this dog from access to her feces. It was deemed of interest to determine whether ingestion of the stools would protect the animal in view of the inadequacies of the diet. This proved to be the case for one hundred and four days, at which time observations were discontinued. The general condition was excellent, the appetite was good, and the dog gained weight during the course of the experiment. Her gastric response was normal.

Comment.—The results cited may be summarized as follows: Dogs subsisting on the Goldberger diet 195 show no loss of gastric function, as evidenced by the response of the gastric glands to a constant stimulation by histamine. Dogs Dolores and Roberta, even when evidencing terminal lethal symptoms considered to be the result of a dietary deficiency, showed normal gastric function. Dog Bozo, after one hundred and twelve days on the Goldberger diet presumably deficient in vitamin G (B_2), continued to secrete normally. On the other hand, after thirty-eight days' subsistence on the casein III ration, which was markedly low in antineuritic vitamin B and which probably contained more vitamin G (B_2) than the Goldberger ration, this dog showed a diminished secretion.

The conclusion to be drawn seems to be that the decreased gastric activity exhibited by three of the four dogs maintained on a diet deficient in the vitamin B complex (part I) was due to a lack of the B (B_1) substance. Administration of this factor rapidly restored the gastric secretory response to normal. Subsistence on the Goldberger diet did not affect the gastric response. However, in view of the uncertainties as to the exact nature of the inadequacies of the Goldberger ration, this study should be repeated, if possible, with a purely artificial diet adequate except with respect to vitamin G (B_2) before this dietary essential can be definitely ruled out as an etiologic factor in producing altered gastric function.

It is doubtful whether one can definitely relate the nervous symptoms so characteristic of lack of the vitamin B complex to a decrease in gastric activity. Dog Dolores continued to secrete in a normal manner and yet severe nervous symptoms developed. On the other hand, dog Petunia, in spite of the fact that she exhibited a complete and true achlorhydria, showed no nervous symptoms. The possibility exists that, even though the gastric response to histamine remained normal, the response of the acid-secreting glands to the less powerful stimulant of food may have been appreciably diminished. Such speculation is supported by the fact that while the experimental diet was used it was unnec-

essary to protect the abdominal muscles surrounding the opening of the pouch from the corrosive action of the escaping gastric juice. The amount of juice escaping was either too small in amount or insufficiently active to produce extensive proteolysis. The fact that actual tests of the gastric juice revealed normal content of pepsin suggests that its diminished hydrolytic power was due to a decrease in the amount of acid secreted. However, it is extremely doubtful whether the glands are inactivated to such an extent that the normal secretion is entirely devoid of hydrochloric acid. It was always possible to demonstrate the presence of free acid in the secretion of dog Dolores without offering such a powerful stimulant as histamine. It is most probable that the gastric glands are capable of producing an acid secretion, although the volume of this secretion is diminished. It is not likely, therefore, that the terminal syndrome characteristic of a deficiency in vitamin B (B_1) is of gastric origin.

SUMMARY AND CONCLUSIONS

The ability of dogs possessing gastric pouches to secrete gastric juice in response to a constant stimulus with histamine during the period of subsistence on a diet lacking the vitamin B complex was studied. The gastric juice was examined for acid and for proteolytic power. Of four dogs fed on artificial diet markedly deficient in vitamin B (B_1), in one a true achlorhydria developed, two evidenced a markedly diminished response to histamine, and one continued to show a normal response; the first three of these animals possessed Pavlov pouches and the fourth dog, a Heidenhain pouch.

Under the assumptions that the variations exhibited by these animals might have been due to varying degrees of a lack of vitamin G (B_2), and that the most outstanding deficiency of the Goldberger 195 diet is with respect to this vitamin, four dogs (two with Pavlov and two with Heidenhain pouches) were fed the Goldberger ration. In two of this group the symptoms described by Goldberger and his co-workers developed without showing any evidence of a loss of gastric function. Coprophagy on the part of a third animal operated to protect the dog against the appearance of such symptoms over a period of one hundred and four days; the fourth dog continued normal for one hundred and twelve days.

The indications of this study are that so far as any diminution of gastric secretion occurs during a regimen of lack of the vitamin B complex, this is due to the absence of the B (B_1) component. However, before it can be definitely stated that the G (B_2) factor plays no etiologic rôle with respect to such altered gastric secretory function, similar experiments should be performed on dogs subsisting on purely artificial diets which lack only vitamin G (B_2).

THE BLOOD IN NORMAL PREGNANCY

I. BLOOD AND PLASMA VOLUMES

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A tremendous number of data on physiochemical changes in the blood during pregnancy have been published, but, with one or two exceptions, the observations reported are based on groups of patients at different periods and not on the same patient throughout pregnancy and the puerperium. Realizing that the normal must be known before abnormalities can be detected, we began, three years ago, a systematic study of the blood of a number of women early in pregnancy and followed them into the puerperium. We also took a number of patients at term and followed them for eight weeks, or longer, after delivery. The reason for the latter series was the impossibility of getting patients before the tenth week of pregnancy, when there had already been some change in the blood, and, furthermore, the difficulty in persuading patients to submit to repeated studies, both before and after delivery, not to mention the possibility of harm to the patient from the procedures used.

Many reports on the volume of blood in pregnancy have been published, and, although the results are conflicting, the belief is prevalent that there is a considerable increase in the blood volume in pregnancy and that, because of this plethora, the pregnant woman can withstand a huge loss of blood at delivery without danger. In a careful review of the literature, we have not been able to find any data which absolutely demonstrate an increase, but we have found a marked lack of uniformity in the reports. Our interest in this subject is based on the following considerations: 1. Is there a sufficient increase in blood volume in pregnancy, as is frequently stated, to permit a loss of from 1,000 to 1,500 cc. of blood at delivery, with no obvious ill effect? 2. The estimations of the blood and plasma volumes form the basis for

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the determination of total hemoglobin, erythrocyte mass, serum protein, fibrin, total base, etc., which will be reported in subsequent studies. 3. If the blood and plasma volumes are increased, it is a phenomenon well worth study in itself.

DeLee [1] stated:

> The total quantity of blood is augmented, especially in the last months, a true plethora existing (Kaboth and Zuntz), a fact proved by Miller by means of the "vital red" method, the volume being between 6 and 9 per cent of the body weight (Bohnen, 7-7.3 per cent), the gain being from 400 to 500 Gm. The need for more blood must be admitted; the addition of the fetus and the fetal circulation, the development of the uterine arteries and veins, the enlargement of the veins of the lower extremities, which are sometimes so great that they appear to be veritable caverns. It would seem that they act as reservoirs and provide for the loss of blood at labor. The veins collapse afterward, but never completely or permanently. This surplusage of blood should not beguile the accoucheur to wastefulness of the vital fluid during delivery.

Williams [2] stated:

> Observations made in my clinic, in 1915, by Miller, Keith and Rowntree seem to show that during pregnancy there is a definite increase in both the plasma and blood volume, which disappears during the puerperium. These conclusions were based upon the injection of known quantities of "vital red" into the circulation, and the colorimetric comparison of the patients' serum with standard preparations of serum colored with the same dye. More extended, but as yet unpublished, observations by Harris in our service during 1922 and 1923 demonstrate that the volume of blood is definitely increased.

Kehrer [3] reviewed the literature up to 1923 and concluded that during the second half and especially during the last two months of pregnancy a marked increase in the blood volume occurs, "a plethora of pregnancy." He stated that in the nonpregnant woman the blood volume ranged from 5 to 6.3 per cent of the body weight, but in pregnancy the range was from 7 to 8.3 per cent.

Denecke [4] reviewed the German literature to 1923, and concluded that the blood volume is increased during pregnancy both in animals and in man (Spiegelberg and Gescheidler [5] found, with Welker's method, that in dogs the blood volume increased from the normal of 7.87 per cent of the body weight to 10.5 per cent in the last half of pregnancy).

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1. DeLee, J. B.: Principles and Practice of Obstetrics, ed. 5, Philadelphia, W. B. Saunders Company, 1928, p. 105.
2. Williams, J. W.: Obstetrics, New York, D. Appleton and Company, ed. 6, 1930, p. 207.
3. Kehrer, E., in Halban, J., and Seitz, L.: Biologie und Pathologie des Weibes, Berlin, Urban & Schwarzenberg, 1925, vol. 6, p. 783.
4. Denecke, G., in Hinselmann, H.: Die Eklampsie, Bonn, Friedrich Cohen, 1924, p. 294.
5. Spiegelberg, O., and Gescheidler, R.: Arch. f. Gynäk. **4**:112, 1872.

Miller, Keith and Rowntree [6] found that normally the amount of blood in cubic centimeters per kilogram ranged from 80 to 91, with an average of 84 cc., but in pregnancy at term the range was from 67 to 115 cc., with an average of 96 cc. The volume plasma varied normally from 48 to 56, with an average of 51 cc. per kilogram, but in pregnancy at term the range was from 38 to 73, with an average of 54 cc. per kilogram. Rowntree and Brown,[7] in their discussion of this work, stated:

> Following delivery there was a large decrease in the absolute blood volume, which was greater than could be accounted for by loss of blood at parturition. The average decrease in blood 7 to 10 days after delivery was 1,100 cc., whereas the average loss of blood at delivery was 300 cc. An increase in the total volume of the blood would be expected in pregnancy because of the fetal circulation. The fact that there is a decrease in the amount of blood following pregnancy in excess of the amount lost by hemorrhage would seem logical on the basis of Lucas and Deering's [8] studies. They found that the volume of blood in the new-born infant varied from 330 to 850 cc. This amount is taken from the maternal circulation. The fetal blood and the amount of blood lost by hemorrhage would account for the difference in blood volume between pregnant and parturient women. This difference was disclosed by Keith and his associates. This study lends confirmation to the belief held in the early part of the nineteenth century that there is a plethora of pregnancy, and confirms the well known clinical observation of the relatively slight danger of loss of blood in the pregnant woman. In absence of data relating to transportation of dye from maternal to fetal blood, a word of caution in the interpretation of such data is necessary. It is possible that pre-edematous states of tissue may be concerned.

Their explanation of the average decrease of 1,100 cc. after delivery is incorrect in part, because (1) there is *no* direct connection between fetal and maternal circulations, and (2) the dye does not go through to the fetus. Therefore, any increase in blood or plasma volume found in pregnancy with a dye method is not due to the fetal circulation.

Schoenholz,[9] in 1929, published an article on the volume of circulating blood in pregnancy, which is based on the largest series of patients so far reported. He identifies his cases by their initials and groups them in a number of tables in which the initials recur repeatedly, so that it is difficult to determine exactly how many patients were studied, and how many determinations were made on each. Approximately forty women were studied, but none earlier than the seventh month.

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6. Miller, J. R.; Keith, N. M., and Rowntree, L. G.: Plasma and Blood Volume in Pregnancy, J. A. M. A. **65**:779 (Aug. 28) 1915.

7. Rowntree, L. G., and Brown, G. E.: The Volume of the Blood and Plasma, Philadelphia, W. B. Saunders Company, 1929.

8. Lucas, W., and Deering, B.: Blood Volume in Infants Estimated by the Vital Dye Method, Am. J. Dis. Child. **21**:96 (Jan.) 1921.

9. Schoenholz, L.: Arch. f. Gynäk. **138**:596, 1929.

Seventeen patients had three antepartum determinations—all after the seventh month—and one postpartum determination on the sixth to the tenth day. These all showed an average antepartum increase of 2.7 per cent. Eight patients similarly studied did not show change in blood volume. He also determined the blood volumes in nine patients, using both carbon monoxide and trypan red, and made the following conclusions: (1) With these methods only the volume of circulating blood and not the total volume of blood is determined; and (2) the former is not a constant, but is dependent on external influences, i. e., temperature and exercise. The colorimetric method deals with the plasma, while the carbon monoxide method deals with the hemoglobin in the erythrocytes. The distribution of the erythrocytes and the plasma varies in the different parts of the vascular system. A comparison of the figures of different investigators has only limited value, but the significance of such investigations remains great in the hands of any one person.

In his figures, which compared with values of nonpregnant women do show a small increase in the volume of circulating blood during pregnancy, are included those for the susceptible circulating fetal blood.

> As a result of its increased hemoglobin content, the fetal blood has a greater capacity for carbon monoxide than the maternal blood. In consequence, the value found for the maternal blood by this method is too high; therefore, the circulating blood volume calculated by the carbon-monoxide inhalation method, which is concerned with the hemoglobin, is certainly not appreciably increased at the end of pregnancy. However, an increase in the plasma volume may be found by the dye methods. The conclusion is to be drawn that a dilution of the blood occurs during pregnancy and from this the fact that pregnant women withstand blood loss better than non-pregnant women is self-explanatory.

In table 1 are listed data on blood volume, together with the method used. We have not included all of the determinations by different observers, but have selected those which were based on the largest series and which seemed representative. It is obvious that one can compare only results by the same method, but even with the same method different results are reported in pregnancy. A study of table 1, together with our collective review of the literature, shows that the problem of whether or not a change in the blood volume occurs in pregnancy is still unsettled. It has also been demonstrated both by us and by others that a standardized method will give results for blood and plasma volumes which will be fairly constant over a long period of time. The marked variations in pregnancy, reported by different investigators, are due, in part, to the fact that all results are based on the weight, which is extremely variable in pregnancy because of the many components which make up the increase (the fetus, placenta, amniotic fluid, increase in the size of the uterus and "physiologic

edema"[10] of pregnancy, altogether amounting to from 7 to 10 or more kilograms). Therefore, to study changes in blood and plasma volume in pregnancy, one must follow the same patient throughout and draw conclusions from a study of the total volumes and not from calculations based on weight or on any function of the latter.

TABLE 1.—*Reported Values for Blood Volume in per Cent of Body Weight*

Authors	Method	Blood Volume, per Cent			Number of Cases
		Non-pregnant	Pregnancy at Term	Puerperal	
Plesch (Ztschr. f. exper. Path. u. Therap. **6**: 380, 1909)	Carbon monoxide	4.7-6.1			
Zuntz (Zentralbl. f. Gynäk. **35**: 1365, 1911)	Carbon monoxide	...	8.4	6.9	6
Schoenholz[9]	Carbon monoxide	6.3	6.7	6.5	40±
Schoenholz[9]	Trypan red	...	9.0	...	9
Fries (Ztschr. f. Geburtsh. u. Gynäk. **59**: 340, 1911)	Antitoxin	7.9	7.4	8.7	10
Mahnert (Arch. f. Gynäk. **116**: 168, 1921)	Refractometric	6.3	8.0	...	10
Gueissaz and Wanner (Schweiz. med. Wchnschr. **52**: 1173 and 1216, 1922)	Refractometric	...	12-15% increase	...	12
Kaboth (Zentralbl. f. Gynäk. **57**: 498, 1923)	Congo red	6.2	6.8	...	20
Neubauer (Deutsche med. Wchnschr. **49**: 520, 1923)	Congo red	6.8	7.4	6.2	8
Koch and Jakobovits (Klin. Wchnschr. **1**: 2518, 1922)	Congo red	5.7	5.4	...	24
Bohnen and Boormann (Arch. f. Gynäk. **126**: 144, 1925)	Congo red	6.4	7.6	...	20
Böttcher (Dissert., Freiburg; quoted by Schoenholz[9])	Trypan red	8.4	9.7	...	10
Hnátek (Zentralbl. f. Gynäk. **51**: 2328, 1927)	Trypan blue	7.8	9.4	8.6	
Rowntree and Brown[7]	Vital red Congo red	Range, 80.2-91.3 Average, 84.2 cc. per Kg. Plasma Range, 47.8-56 Average, 50.5 cc. per Kg.			
Miller, Keith and Rowntree[6]	Vital red	...	9.6% Range, 67-115 Average, 91 cc. per Kg. Plasma Range, 38.1-72.7 Average, 54.5 cc. per Kg.	... 85.7	13

We have not been able to find any work in which this was done, for all of the reports are based on a number of observations made on different women at the various periods of pregnancy and are calculated

10. Practically all pregnant women have an increased amount of body water, which is usually manifested late in pregnancy by one or more of the following: pitting edema of the lower extremities, excessive and rapid increase in weight, a marked diuresis (negative water balance) after delivery or death of the fetus, and —or—a marked loss of weight post partum.

on the weight, being reported either as percentage of body weight or as cubic centimeters per kilogram.

For a study such as we contemplated only two methods were adaptable: (1) the dye method, in which the plasma volume is determined, and (2) the carbon monoxide method, in which both the circulating hemoglobin and myohemoglobin are determined. The latter method was undesirable because it would include the fetal blood, and no correction could be made because of the varying hemoglobin and constantly changing oxygen capacity of this fetal blood. We, therefore, chose the dye method, realizing that no method will give the absolute plasma or blood volume, but believing that one can, with proper technic, obtain consistent results. In table 2 we give data on blood and plasma volumes, hematocrit readings etc., on ourselves. The small variations indicate that the blood volume is maintained within

TABLE 2.—*Repeated Determinations of Blood Volume on Normal Persons*

			Hemato-crit,	Blood			Plasma		
Name	Date	Weight, Kg.	per Cent	Volume, Cc.	Cc. per Kg.	Cc. per Sq. M.	Volume, Cc.	Cc. per Kg.	Cc. per Sq. M.
W. J. D.	1/22/31	87.7	50	5,752	65.5	2,930	2,876	32.8	1,460
	2/ 3/31	87.7	50	5,614	64.0	2,860	2,807	32.0	1,430
C. W.	1/22/31	59.0	46.3	4,350	73.8	2,650	2,349	39.8	1,440
	2/ 9/31	59.0	45.0	4,450	75.4	2,710	2,448	41.5	1,490
	12/24/32	59.0	44.0	4,571	77.5	2,780	2,560	43.3	1,560

narrow limits. The results of two determinations of plasma volume on nine normal men, by Keith, Rowntree and Geraghty,[11] showed an average variation between the two determinations of 1.5 per cent. Rowntree and Brown,[7] in normal persons over a period of from two to fourteen days, reported an average variation of 5.8 per cent; whereas, over periods of from one to twenty-four months, the mean variation was 8.6 per cent. Therefore, changes in volume, to be significant, must be plus or minus 5 per cent. We have disregarded changes unless they were greater than 5 per cent.

We planned to obtain volumes on the same patient at monthly intervals throughout pregnancy, but found that certain women (six in number) were susceptible to the dye (vital red), in that the skin of the face, especially below the eyes, and of the arms and trunk was stained red (from three injections); the discoloration was still present nine weeks after delivery. Our plan was, therefore, modified, and three determinations were obtained ante partum and from one to three, post partum. Congo red was substituted for vital red, and in

11. Keith, N. M.; Rowntree, L. G., and Geraghty, J. F.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547 (Oct.) 1915.

over three hundred determinations no further difficulties have been encountered. We started with twenty-five patients, early in pregnancy, but have been able to follow completely through pregnancy and post partum only fifteen, designated as series A. Since practically all of our patients were seen first after the tenth week, we obtained determinations on other patients before delivery and also from three to eight weeks post partum, believing that at this time the blood and plasma volumes should be normal. The latter group is designated as series B. Our conclusions are based on the data obtained by repeated determinations of the blood volume on the same patient. Thus, we had twenty patients with two determinations, sixteen with three, eighteen with four, and four with five determinations.

METHOD

We used Keith and Rowntree's method, in which the plasma volume is determined by means of vital red, and the blood volume calculated from it. The method was first used as outlined by them, but we soon saw that a given amount of solution could be injected more accurately than varying amounts. Therefore, either 8 or 10 cc. of the dye, depending on the patient's weight, was injected. As an anticoagulant for determining cell volume, heparin was used. In the original method approximately twice the amount of dye used by us was injected, and the determination was made by diluting the plasma 1 : 4 and setting the colorimeter at 10. We injected only half the amount of dye, diluted 1 : 4, but set the colorimeter at 20. The results were identical, but the colorimetric error was considerably reduced. The syringes were standardized and were used for nothing else. The pipets used for the dilutions were certified, and the standard for each colorimeter determination was made from a portion of the same dye which had been injected. Most of the determinations were made with the patient lying on her back, but some were made in the sitting position. There was a period of rest of at least twenty minutes before the dye was injected. The complete determination of blood volume was always carried out by one of us; therefore, we were able to prevent the occurrence of hemolysis which would have made the determination valueless. A recent article by Graff and Clarke,[12] on studies in which the spectroscope was used to determine the presence of hemoglobin, is a valuable contribution, but with proper technic one can prevent the occurrence of hemolysis.

For purposes of comparison, volume figures must be reported on some basis, which may be weight, surface area, etc., but, as we have pointed out, with a variable weight the figures have no real significance. In tables 3 and 4 we have grouped our results on a basis of cubic centimeters of blood and plasma per kilogram of uncorrected body weight. The wide range from 53 to 113 cc. of blood per kilogram and from 32 to 71 cc. of plasma per kilogram shows definitely that changes in the amount of blood and plasma per kilogram have no significance when the

12. Graff, S., and Clarke, H. T.: Determination of Plasma Volume, Arch. Int. Med. **58**:808 (Nov.) 1931.

weight is changing also. We have also made similar calculations on a corrected body weight (deducting a theoretical weight for fetus, amniotic fluid and placenta) and, likewise, the range is still great. The figures in the row marked "Total" designate the number of patients in the period of pregnancy shown who had the volumes per kilogram indicated, and

TABLE 3.—*Cubic Centimeters of Blood per Kilogram: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
Cc. per Kg.	8-15	16-25	26-35	36-40	2-6	10-25	8 Wks.
50- 59	4	..	1	3	2	1	..
60- 69	5	1	5	9	7	11	2
70- 79	5	5	4	8	5	9	3
80- 89	4	1	12	25	6	6	6
90- 99	5	2	4	6	2	7	..
100-109	2	..	1	3	1	4	..
110-114	..	..	..	1	1	3	..
Total	25	9	27	55	24	41	11
Mean							
Total cases	77.3±2.1	79.5	80.4±1.6	80.9±1.2	77.0±2.0	82.1±1.9	
Standard deviation	15.9		11.6	13.3	14.8	18.0	
Series A	76		76	76.4	75.3	84.4	
Series B	....		....	81.1	74.2	77.2	79.2

TABLE 4.—*Cubic Centimeters of Plasma per Kilogram: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
Cc. per Kg.	8-15	16-25	26-35	36-40	2-6	10-25	8 Wks.
30-39	5	1	2	6	..	3	1
40-49	10	5	11	21	12	20	5
50-59	8	3	12	21	11	11	5
60-69	2	..	2	7	1	6	..
70-74	..	..	..	..	..	1	..
Total	25	9	27	55	24	41	11
Mean							
Total cases	47.3±1.2	47.5	49.7±1.0	49.8±0.8	49.0±0.8	50.1±1.1	
Standard deviation	9.2		7.4	8.3	5.8	10.7	
Series A	45.4		47.2	47.2	46.6	50.2	
Series B	....		....	50.4	47.0	48.4	49.2

the means per kilogram are calculated for these different groups. The standard deviations and the difference between means for the various periods of the "total cases" have been calculated, and the latter figures indicate that the variations of the blood and plasma volumes per kilogram are of no significance.

The figures for both blood and plasma are lower than those reported by Miller and his co-workers. Series A shows no appreciable change ante partum, but a slight increase at from ten to fifteen days post partum, which is just the opposite of Miller's findings. These calculations are

based on weight and are, therefore, misleading because figures for total blood volume (table 6) indicate that there was no appreciable change in blood volume in five cases (the apparent increase was due to loss of weight incident to delivery), a decrease in five and an increase in three. Total plasma volumes showed that there was no change in two cases, a decrease in nine and an increase in two. With the general stimulus to metabolism and the maturing of the woman incident to pregnancy, one would expect that patients with low blood and plasma volumes before pregnancy would tend to retain a portion of the increase. Series B shows a marked drop at from ten to fifteen days post partum, with a return at eight weeks to a figure only slightly below that found in pregnancy. However, at eight weeks, only one of the patients had a total blood volume greater than the one obtained at term. All but two (no change)

TABLE 5.—*Range of Variations of Blood and Plasma Volumes*

Increase or Decrease, per Cent	Number of Patients Showing Increase Above Initial Determination				Number of Patients Showing Decrease Below Last Antepartum Determination							
	26-35 Weeks		36-40 Weeks		2-6 Days		10-15 Days		18-26 Days		8-17 Weeks	
	B.*	P.†	B.	P.	B.	P.	B.	P.	B.	P.	B.	P.
6-9	1	1	2	..	4	2	2	6	1	..	..	..
10-19	3	4	1	4	4	5	5	9	1	2	7	6
20-29	4	5	1	1	3	7	7	5	2	2	..	1
30-39	1	1	3	2	6	1	5	3	..	..	..	..
40-49	..	..	1	2	..	..	..	1	..	..	1	1
50-59	1	1	1	..	..	..	..	..	..	..	..	..
60-69	1	1	..	..	..	..	..	..	..	..	..	..
90	..	..	1	..	..	..	..	..	..	..	..	..
106	..	..	..	1	..	..	..	..	..	..	..	..

* B. = blood.
† P. = plasma.

of the total plasma volumes showed decreases. Thus, studies on the blood after delivery must be made after a longer interval than two weeks, if they are to be of value.

Table 5 shows the variations in blood and plasma volumes in percentage of increase and decrease, together with the number of cases showing the various changes. All antepartum values are divided by the first one obtained and the quotient multiplied by 100. Thus all data are converted to a common basis, and changes in different patients can then be compared. Postpartum values were converted similarly, but the determination at term was used as the divisor. In other words, the first antepartum volume is assumed to be 100 per cent, and the subsequent determinations are expressed in percentage of increase or decrease relative to it. Similarly, postpartum volumes are expressed in percentage of decrease or increase, relative to the determination at term, which is assumed to be 100 per cent. The cases showing variations of 5 per cent or less are classed as those with no appreciable change. These results

indicate that in the majority of cases there is a marked increase in blood and plasma volumes in pregnancy with a commensurate decrease after delivery. More cases showed larger increases in plasma volume than in blood volume. Increases in blood and plasma volumes of 30, 40, 60 per cent, etc., seem improbable and suggest that either a mistake was made in the determination or the patient had developed a tolerance for the dye. However, the increases in each patient were consistent; likewise, this same patient showed marked decreases post partum, thus demonstrating that the method was not at fault.

Table 6 gives essential data on series A, that is, on those patients who were followed throughout pregnancy and the puerperium. The pregnancy and puerperium were normal, unless the notes under "Comment" indicate otherwise. Changes in blood and plasma volumes, at least in these patients, had no effect on the labor, size of the baby, amount of milk or incidence of infection. The figures in column 2, which were derived by calculations similar to those described in the preceding paragraph, show the individual variations in blood and plasma volumes in per cent. The patients who had low volumes per kilogram (columns 3 and 7) when first seen usually had the greatest increase, and, as a rule, they tended to retain some of this excess blood and plasma after delivery, with the result that the volumes per kilogram were closer to the normal than were the first figures. This is shown best in patients 1, 5, 7 and 9. Three of the patients showed a decrease of blood of more than 1,000 cc. after delivery, but the majority showed either an increase or no change, thus differing from those of Miller and his co-workers. It is evident that in order to obtain consistent and significant results determinations must be made at a later date in the puerperium. The data on the amount of blood per square meter are included for completeness. Essentially, the same changes take place if the volumes are calculated on the surface area, as would be expected, because one of the factors used in calculating the surface area is the weight. Rowntree and Brown [7] stated that pregnancy is characterized by a "simple hypervolemia" (increase in blood volume with a normal ratio of cell and plasma) which develops in the last month and lasts from two to three weeks post partum. Our data indicate that pregnancy is characterized by an "oligocythemic hypervolemia" (increase in blood volume with a reduced number of cells—hematocrit figures are given in a subsequent paper), which develops as early as the beginning of the second trimester, reaches a maximum at term and fluctuates somewhat for the first three weeks after delivery, but the general trend is a return to the normal "simple normovolemia." The gains in blood and plasma shown by most patients are another indication of the profound changes produced by pregnancy in the maternal organism.

TABLE 6.—*Data on Patients Followed Throughout Pregnancy and the Puerperium (Series "A")*

Patient, Gravida, Race,* Age	Date	Period of Gestation or Post Partum	Comment: Loss of Blood at Delivery†	Wt., Kg.	Surface Area, Sq. M.	Blood: Total Volume		Blood: Cc. per Kg.	Blood: Cc. per Sq. M.	Plasma: Total Volume		Plasma: Cc. per Kg.	Plasma: Cc. per Sq. M.
						Cc.	Change, %			Cc.	Change, %		
						1	2	3	4	5	6	7	8
1	1/ 7/31	13 wks.	200±	46.3	1.48	3,113	...	69	2,100	1,868	...	40	1,260
II	4/22/31	29 wks.		55.9	1.59	5,009	160	91	3,130	3,106	166	56	1,950
W	8/ 3/31	40 wks.		59.5	1.64	5,930	190	100	3,620	3,855	206	65	2,350
20	8/14/31	12 days		50.4	1.53	5,520	93	110	3,610	3,478	90	69	2,270
2	2/25/31	14 wks.	200±	77.9	1.82	4,585	...	59	2,570	2,935	...	38	1,610
I	5/ 7/31	30 wks.		81.0	1.85	4,951	108	61	2,670	3,367	115	42	1,820
W	8/20/31	40 wks.		80.9	1.85	4,968	108	62	2,680	3,478	119	43	1,880
23	9/ 1/31	12 days		73.6	1.77	4,643	93	63	2,620	3,018	86	41	1,700
3	1/14/31	15 wks.	200±	53.0	1.66	5,221	...	98	3,150	2,978	...	56	1,790
I	5/13/31	30 wks.		61.1	1.70	6,415	123	105	3,770	3,720	125	61	2,190
W	6/27/31	40 wks.		63.5	1.73	5,444	104	86	3,140	3,440	116	54	1,990
23	7/ 7/31	12 days		53.0	1.66	5,601	103	106	3,380	3,137	91	59	1,890
4	2/ 4/31	14 wks.	200±	92.2	2.07	5,369	...	58	2,600	3,007	...	53	1,450
VII	5/13/31	27 wks.		91.7	2.07	6,318	118	69	3,050	3,669	122	40	1,770
W	7/30/31	40 wks.		87.0	1.99	7,143	133	82	3,680	4,000	133	46	2,010
30	8/10/31	14 days		82.7	1.95	5,750	81	70	2,940	2,990	75	36	1,530
5	1/21/31	12 wks.	Cesarean section 200±	53.6	1.45	3,681	...	69	2,540	2,135	...	40	1,470
II	5/13/31	28 wks.		59.5	1.52	4,448	121	75	2,920	2,758	129	75	1,810
W	8/ 4/31	39 wks.		60.0	1.52	4,822	131	80	3,170	2,990	140	80	1,970
25	8/20/31	14 days		52.5	1.44	5,932	123	113	4,120	3,678	123	113	2,550
6	2/24/31	14 wks.	200±	45.9	1.41	3,438	...	75	2,420	2,201	...	48	1,560
I	5/26/31	27 wks.		54.8	1.52	4,448	129	81	2,920	2,758	116	50	1,810
W	8/25/31	40 wks.		63.5	1.61	5,091	148	80	3,106	3,106	141	49	1,930
19	9/ 4/31	11 days		56.0	1.53	5,015	99	90	3,280	2,909	94	52	1,900
7	10/22/30	14 wks.	150 ml.	107.2	2.14	5,756	...	54	2,690	3,454	...	32	1,610
VI	1/16/31	30 wks.		112.5	2.18	5,910	103	53	2,710	3,783	110	34	1,730
W	3/26/31	40 wks.		114.6	2.20	6,471	112	56	2,940	3,883	112	34	1,760
31	4/ 2/31	5 days		100.3	2.08	6,250	97	63	3,000	4,000	103	40	1,920
	4/10/31	13 days		100.4	2.08	7,838	121	78	3,770	4,938	127	49	2,370
8	12/ 4/30	14 wks.	200±	92.9	2.05	6,643	...	72	3,240	4,318	...	46	2,100
III	3/11/31	28 wks.		103.5	2.15	6,269	95	61	2,910	3,950	92	38	1,840
C	4/30/31	40 wks.		108.9	2.20	7,050	106	65	3,200	4,301	100	39	1,950
30	6/ 8/31	11 days		100.0	2.11	5,395	77	54	2,560	3,669	85	37	1,740
9	10/29/30	14 wks.	200±	50.0	1.45	3,968	...	79	2,740	2,500	...	50	1,720
I	2/18/31	29 wks.		58.8	1.55	4,800	121	82	3,100	3,168	127	54	2,040
C	4/13/31	40 wks.		60.0	1.56	5,209	131	87	3,380	3,232	129	54	2,130
21	4/15/31	3 days		55.8	1.51	4,914	93	88	3,270	3,047	94	55	2,020
	4/24/31	12 days		52.5	1.48	5,106	98	97	3,480	2,962	92	56	2,000
10	9/ 2/30	20 wks.	200±	71.8		5,341		74		3,205		45	
I	9/23/30	23 wks.		72.0		4,540		63		2,815		39	
W	12/ 4/30	36 wks.		75.5		6,428	120	85		3,600	113	48	
26	12/13/30	3 days		70.3		5,301	83	75		3,181	88	45	
11	4/ 1/31	15 wks.	200±	67.2	1.70	5,830	...	87	3,420	3,440	...	51	2,020
I	6/23/31	28 wks.		73.8	1.76	5,763	99	78	3,270	3,516	102	48	2,000
W	9/14/31	39 wks.		76.5	1.79	5,763	99	75	3,220	3,516	102	46	1,970
22	9/28/31	12 days		68.1	1.71	6,107	107	91	3,600	3,298	94	48	1,930
12	2/ 9/31	9 wks.	200±	61.3	1.69	5,213	...	85	3,080	3,076	...	50	1,820
I	6/16/31	27 wks.		80.0	1.90	6,783	130	85	3,570	4,102	133	51	2,160
C	9/17/31	40 wks.		86.3	1.95	4,901	94	57	2,510	3,137	102	36	1,610
28	9/28/31	11 days		75.6	1.85	4,961	101	66	2,680	3,076	97	41	1,660
13	1/28/31	11 wks.	200±	68.1	1.78	6,168	...	91	3,460	3,578	...	52	2,000
VIII	6/ 3/31	29 wks.		75.4	1.85	6,046	98	80	3,270	3,809	106	50	2,060
C	8/26/31	40 wks.		71.5	1.81	5,554	90	78	3,060	3,555	99	50	1,960
37	9/ 4/31	11 days		65.6	1.74	5,686	102	87	3,270	3,298	93	50	1,890

* In this and the following table W indicates the white race; C, the colored race.
† In this and the following table the loss of blood at delivery, unless excessive or measured, is assumed to be approximately 200 cc.

Table 7 gives essential data on series B, comprising patients who were followed up to eight weeks post partum. The data have been arranged similarly to those in the preceding table. Up to three weeks post partum

TABLE 7.—*Data on Patients Followed from Term to Eight Weeks Post Partum (Series "B")*

Patient, Gravida, Race, Age	Date	Period of Gestation or Post Partum	Comment: Loss of Blood at Delivery	Weight, Kg.	Blood: Total Volume Cc.	Blood: Total Volume Change, %	Blood: Cc. per Kg.	Plasma: Total Volume Cc.	Plasma: Total Volume Change, %	Plasma: Cc. per Kg.
					1	2	3	4	5	6
31	10/13/31	39 wks.	200±	67.0	6,557	..	98	4,000	..	60
I, C	10/27/31	12 days		56.5	4,418	67	80	2,563	64	45
15	12/ 9/31	8 wks.		53.6	5,316	81	99	2,977	74	55
32	9/22/31	40 wks.	1,020	65.0	5,555	..	85	3,333	..	51
I	9/29/31	3 days		58.0	3,789	68	65	2,577	77	44
W	10/ 8/31	12 days		55.5	4,284	77	77	2,742	82	49
27	11/25/31	8 wks.		60.5	4,545	82	75	2,727	82	45
33	11/ 5/31	40 wks.	75	103.4	5,701	..	55	3,877	..	38
II	11/13/31	3 days		90.0	5,037	104	66	3,800	98	42
W	11/29/31	19 days		87.5	5,396	95	62	3,454	89	40
29	1/13/32	9 wks.		89.2	6,115	107	69	4,036	104	45
34	12/18/31	40 wks.	550	72.2	6,000	..	83	3,600	..	50
I	1/16/32	12 hrs.		64.7	4,161	..	64	2,622	..	41
C	1/20/32	5 days		63.1	3,876	65	61	2,597	78	41
25	3/10/32	8 wks.		64.5	5,196	87	80	3,168	88	49
35	9/ 9/31	36 wks.	400±	68.1	5,085	..	74	3,153	..	46
II, W	10/11/31	11 days		61.5	4,089	80	66	2,781	88	45
24	11/25/31	8 wks.		58.6	4,280	84	73	2,654	84	45
36	9/20/31	40 wks.	200±	68.4	4,648	..	68	3,161	..	46
I	(in labor)									
C	9/23/31	3 days		63.0	4,700	101	75	3,479	110	55
25	10/ 1/31	12 days		56.8	3,629	78	64	2,722	86	48
	11/18/31	8 wks.		54.5	4,453	96	82	3,162	100	58
37	9/13/31	38 wks.	200±	82.0	7,870	..	96	4,880	..	60
III, W	9/26/31	12 days		73.0	4,786	61	65	2,920	60	40
30	11/18/31	8 wks.		75.0	6,392	81	85	4,155	85	55
39	9/ 4/30	39 wks.	200±	67.5	5,610	..	83	3,254	..	48
I, W	9/18/30	11 days		51.9	3,613	64	70	2,168	67	42
17	1/31/31	17 wks.		50.0	3,181	57	64	1,909	59	38
40	11/15/31	40 wks.	50	54.0	4,584	..	85	2,934	..	54
III	11/18/31	3 days		48.2	4,867	106	101	2,823	96	59
C	12/ 9/31	25 days		46.8	4,570	100	98	2,925	100	62
28	1/12/32	8 wks.		47.2	3,883	85	82	2,408	82	51
43	10/22/31	38 wks.	60	72.2	6,083	..	84	3,711	..	51
I	Del. 27									
C	10/31/31	5 days		63.5	4,875	80	77	2,633	71	41
17	11/14/31	19 days		62.2	7,031	115	113	4,078	110	65
	12/22/31	8 wks.		61.9	5,120	84	83	3,175	86	51

the changes in blood and plasma volumes were variable, but at eight weeks almost all of the patients demonstrated a decided decrease in the total blood and plasma volumes; however, the volumes per kilogram either tended to remain constant or showed an increase toward the normal average.

Table 8 is arranged to show antepartum changes in the blood and plasma volumes. The calculations used are given in a previous paragraph (table 5). The table is detailed, and the data prove conclusively that there is an increase in blood and plasma volumes in pregnancy. This

TABLE 8.—*Average Changes in Blood and Plasma Volume Calculated on Variations in Total Volume, Using the Initial Determination as One Hundred per Cent for the Antepartum Period*

	Blood Volume		Plasma Volume	
	Number of Cases	Volume Change, per Cent	Number of Cases	Volume Change, per Cent
From 26 to 35 weeks' gestation:				
Average increase in all cases	17	15.8	17	18.2
Average increase in those showing increase	11	27.4	13	26.0
Average decrease in those showing decrease	2	14.0	3	10.0
No change in volume	4	0	1	0
From 36 to 40 weeks' gestation:				
Average increase in all cases	14	22.5	14	24.8
Average increase in those showing increase	10	33.0	10	34.4
Average decrease in those showing decrease	2	8.0	..	....
No change in volume	2	0	4	0

TABLE 9.—*Average Changes in Blood and Plasma Volumes Calculated on Variations in Total Volume, Using the last Antepartum Determination as One Hundred per Cent for the Postpartum Period*

	Blood Volume		Plasma Volume	
	Number of Cases	Volume Change, per Cent	Number of Cases	Volume Change, per Cent
From 2 to 6 days post partum				
Average decrease in all cases	24	13.5	24	11.0
Average decrease in those showing decrease	17	20.6	14	20.5
Average increase in those showing increase	2	14.5	2	15.5
No change in volume	5	0	8	0
From 10 to 25 days post partum				
Average decrease in all cases	40	10.2	40	10.0
Average decrease in those showing decrease	23	22.0	28	18.5
Average increase in those showing increase	7	14.8	6	19.8
No change in volume	10	0	6	0
From 8 to 17 weeks post partum				
Average decrease in all cases	10	15.6	10	15.6
Average decrease in those showing decrease	8	19.9	8	20.0
Average increase in those showing increase	1	7.0	..	....
No change in volume	1	0	2	0

increase is most marked in the last half of pregnancy, reaching a maximum at term. The increase in blood and plasma volume varies from 20 to 25 per cent.

Table 9 lists postpartum changes, and these data indicate that the decrease in blood and plasma volume after delivery is approximately the same as the antepartum increase; therefore, the conclusion that there is an increase in blood and plasma volumes at term is confirmed.

COMMENT

What is the need of an increase in blood and plasma volumes during pregnancy? Is it to fill the vessels of the uterus and lower extremities, as suggested by DeLee? If the latter is true, old multiparas, because of the increased number and size of the varicosities, should have larger volumes of blood and plasma than young primiparas, but this is not found. For example, patient 13, who was an octigravida, 37 years of age, with varicose veins, had the respective volumes given in table 4 and showed a decrease rather than an increase in blood volume at term. Patient 1 (gain of 90 per cent blood and 106 per cent plasma), patient 4 (gain of 33 per cent blood and plasma), patient 5 (gain of 31 per cent blood and 40 per cent plasma) and patient 46 (gain of 48 per cent blood and 41 per cent plasma) not only had no visible varicosities, but were in excellent physical condition and yet they experienced marked increases in volume. A possible explanation is that some increases in blood and plasma are necessary to supply the increase in maternal tissue (uterus and actual increase in weight incident to maturity, which is maintained after delivery), but the major portion is required to permit proper gaseous metabolism on the part of the fetus, involving as little extra work on the part of the mother as possible.

The fetal blood at birth has an oxygen capacity of 32 per cent by volume, but by the tenth day it has decreased to 23 per cent by volume (Peters and Van Slyke). This high capacity is necessary because the hemoglobin in the umbilical vein (arterial blood) is only 63 per cent saturated, whereas, normally, arterial hemoglobin is 95 per cent, and venous, 71 per cent saturated with oxygen. The blood in the placental sinuses is probably more like venous than arterial blood. Sufficient oxygen could be brought to the placenta, either by increasing the blood flow per minute, which would allow less time for gaseous diffusion, increasing the concentration of hemoglobin in the cell, or by increasing the number of erythrocytes. The latter would result in an increase in the viscosity of the blood and require more work by the heart. However, if both cells and plasma were increased proportionately, there would be no increase in viscosity, and gaseous exchange would be normal. The blood and plasma do increase, but the increase in plasma is greater, thus reducing the viscosity, and, as a result, the peripheral resistance may be diminished, thereby increasing the cardiac output. The result is that more blood is circulating, and more time is permitted for proper fetal respiration. Dreysel [13] and Jagie [14] found that the hearts of pregnant and puerperal women weighed more than those of normal

13. Dreysel, quoted by Williams.[2]

14. Jagie, N., in Halban, J., and Seitz, L.: Biologie und Pathologie des Weibes, Berlin, Urban & Schwarzenberg, 1926, vol. 5, p. 388.

persons, which, in view of the slight hypotension and normal heart rate found in this condition, would indicate an increased output of blood for each contraction. Stander and his co-workers [15] have demonstrated both in dogs and in man that in pregnancy there is an increase in cardiac output, amounting to over 50 per cent of the normal value. Thus there is the mechanism to take care of an increased volume. It will be difficult to prove this theory, but in cardiac decompensation and severe anemia, cases in which the fetus would be most likely to suffer from an insufficient supply of oxygen, the fetal mortality is extremely high.

SUMMARY

The published reports on blood and plasma volumes in pregnancy are conflicting because they are based on the patient's weight, which not only is not constant, but is subject to marked variations in short intervals of time (fetus, placenta, amniotic fluid, increase in size of the uterus and physiologic edema of pregnancy, altogether amounting to from 7 to 10 Kg. or more). Furthermore, from 3 to 6 Kg. (fetus and amniotic fluid) of the increase has no direct connection with the maternal vascular system and would, therefore, have no influence in producing an increase in volume. Because of marked physiochemical changes in the blood in pregnancy, which are intimately associated with the well-being of the patient, it was thought important to determine definitely what the normal changes in blood and plasma volumes are in pregnancy. The same patient was followed throughout pregnancy and the puerperium, and the variations were calculated on total changes in volume. Determinations of blood and plasma volumes were made with a dye method (congo red) which, although it probably does not give the true value, does give consistent results with the proper technic. As the determination of percentage changes was the most important part of the study, the data reported are of significance.

The theory is advanced that the increase in blood and plasma volumes is a part of the mechanism by which gaseous exchange between mother and fetus is carried out with a minimal expenditure of work.

CONCLUSIONS

Previously reported values for blood and plasma volumes in pregnancy are at variance with each other, and the results are inconclusive because of the different methods used and the method of calculation. The volumes are reported either in cubic centimeters per kilogram or in percentage of body weight, either of which is unreliable because of the constantly changing weight in pregnancy.

15. Stander, H.; Duncan, E., and Sisson, W.: Am. J. Obst. & Gynec. **11**:44, 1926. Stander, H., and Cadden, J. F.: ibid. **24**:13, 1932.

Determinations of the blood and plasma volumes were made on various groups of women for the different periods of pregnancy. The cubic centimeters per kilogram and the means for the different periods were calculated, and although there is a slight increase at term, statistical analysis indicates that the changes are of no significance.

Similar studies in which the same women were followed throughout pregnancy and the puerperium indicate that the following changes occur:

1. The blood and plasma volumes begin to increase in the first trimester, and by the thirteenth week the gain amounts to 16 per cent and 18 per cent, respectively.

2. At term the average increase in the blood volume is 23 per cent and the plasma 25 per cent. This change is designated an "oligocythemic hypervolemia." Although this increase seems large, losses of blood of 700 cc. or more are at once manifested in measurable reductions in volume. The pregnant woman survives losses of blood which would be fatal if she were not pregnant, partly because of the increase in blood volume, but more particularly because of the tremendous amount of fluid in her tissues.

3. At eight weeks post partum there is an average decrease of 16 per cent for both blood and plasma volumes. This does not quite equal the increase, but, since most of the patients weigh more after pregnancy, the discrepancy is explained.

4. The increase in blood and plasma volumes is not merely to fill vessels but is probably a part of the mechanism required to permit proper fetal respiration.

RHEUMATOID (ATROPHIC) ARTHRITIS

BACTERIOLOGIC CULTURES OF SYNOVIAL FLUID AND OF TISSUES

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During the past several years various attempts to isolate a micro-organism of etiologic significance from the synovial fluids, tissues or blood of patients with rheumatoid arthritis (atrophic, deforming arthritis) have yielded peculiarly inconsistent results. In the hands of most investigators a rather high percentage of cultures has remained sterile, while in the positive cultures a variety of micro-organisms have been obtained. While streptococci have most frequently been isolated by various groups of laboratory workers, other micro-organisms have also been obtained, and the results as a whole are not at all comparable as to either the kind or the number of organisms isolated. The one exception to this general statement is found in the reports of Gray and Gowen and of Gray, Fendrick and Gowen,[1] who repeated and confirmed the cultural work of Cecil, Nicholls and Stainsby, using a modification of the last author's technic.

Cecil, Nicholls and Stainsby[2] reported the frequent isolation of streptococci from the blood (in from 61.5 to 62.3 per cent) and joints (67.3 per cent) of patients with rheumatoid arthritis. The majority of these streptococci fell into a more or less homogeneous group, and were considered to be attenuated hemolytic forms. Gray and his co-workers reported the isolation of a streptococcus which "resembled the one Cecil considered specific for rheumatoid arthritis" in 62 per cent of their cultures from the blood or joints (61 per cent in their second report).

In contrast to the close approximation of these results, the majority of investigators—several of whom have attempted to carry out the technic described by Cecil, Nicholls and Stainsby—have recorded the isolation of a variety of organisms. Those most frequently reported

From the Laboratory Division, Hospital for Joint Diseases.

1. Gray, J. W., and Gowen, C. H.: The Role of the Streptococcus in Arthritis Deformans, Am. J. M. Sc. **182**:682 (Nov.) 1931. Gray, J. W.; Fendrick, E., and Gowen, C. H.: Rheumatic Fever and Rheumatoid Arthritis from the Laboratory Point of View, Texas State J. Med. **28**:317 (Sept.) 1932.

2. Cecil, R. L.; Nicholls, E. E., and Stainsby, W. J.: The Bacteriology of Blood and Joints in Chronic Infectious Arthritis, Arch.Int.Med. **43**:571 (May) 1929; The Etiology of Rheumatoid Arthritis, Am. J. M. Sc. **181**:12 (Jan.) 1931.

have been hemolytic, indifferent or green-producing streptococci, staphylococci and diphtheroid bacilli.[3] The positive cultures obtained usually represented a relatively small percentage of the total number of cultures attempted. The most consistent feature of these reports is the inconsistency of the results.

In the Hospital for Joint Diseases and its clinic, where patients presenting a large variety of conditions of the joints are under treatment, opportunity has been afforded of culturing synovial fluids and tissues, not only from cases of rheumatoid arthritis, but from cases of many other infectious and noninfectious conditions of the joints. The

3. (*a*) Richards, J. H.: Bacteriologic Studies in Chronic Arthritis and Chorea, J. Bact. **5**:511 (Sept.) 1920; Bacteremia Following Irritation of Foci of Infection, J. A. M. A. **99**:1496 (Oct. 29) 1932. (*b*) Billings, F.; Coleman, G. H., and Hibbs, W. G.: Chronic Infectious Arthritis. Statistical Report with End-Results, J. A. M. A. **78**:1097 (April 15) 1922. (*c*) Crowe, H. W.: Bacteriology and Surgery of Chronic Infectious Arthritis, New York, Oxford University Press, 1927. (*d*) Hadjopoulos, L. G., and Burbank, R.: A Preliminary Study Bearing on the Causative Factors of Multiple Infective Arthritis, J. Bone & Joint Surg. **9**:278 (April) 1927. (*e*) Forkner, C. E.; Shands, A. R., and Poston, M. A.: Synovial Fluid in Chronic Arthritis: Bacteriology and Cytology, Arch. Int. Med. **42**:675 (Nov.) 1928. (*f*) Poston, M. A.: Gland Cultures in Infectious Arthritis, J. A. M. A. **93**:692 (Aug. 31) 1929. (*g*) Key, J. A.: Pathogenic Properties of Organisms Obtained from Joints in Chronic Arthritis, Proc. Soc. Exper. Biol. & Med. **26**:863 (June) 1929. (*h*) Shands, A. R.: Synovial Fluid in Infectious and Neuropathic Arthritis, South. M. J. **23**: 818 (Sept.) 1930. (*i*) Margolis, H. M., and Dorsey, A. H. E.: Bacteriology of the Blood in Chronic Infectious Arthritis, J. Infect Dis. **46**:442 (June) 1930; Chronic Arthritis: Bacteriology of Affected Tissues, Arch. Int. Med. **46**:121 (July) 1930. (*j*) Nye, R. N., and Waxelbaum, E. A.: Streptococci in Infectious (Atrophic) Arthritis and Rheumatic Fever, J. Exper. Med. **52**:885 (Dec.) 1930. (*k*) Klugh, G. F.: Streptococci from Blood Cultures in Arthritis, South. M. J. **24**:706 (Aug.) 1931. (*l*) Bernhardt, H., and Hench, P. S.: Bacteriology of the Blood in Chronic Infectious Arthritis, J. Infect. Dis. **49**:489 (Dec.) 1931. (*m*) Dawson, M. H.; Olmstead, M., and Boots, R. H.: Bacteriologic Investigations on the Blood, Synovial Fluid. and Subcutaneous Nodules in Rheumatoid (Chronic Infectious) Arthritis, Arch. Int. Med. **49**:173 (Feb.) 1932. (*n*) Cadham, F. T.: A Discussion on the Etiology and Specific Treatment of Arthritis, Canad. M. A. J. **26**:287 (March) 1932. (*o*) Strauss, A.: Problems in the Relation of Streptococci and Diphtheroid Bacilli to Chronic Infectious Arthritis, Virginia M. Monthly **58**:801 (March) 1932. (*p*) Clawson, B. J., and Wetherby, M.: An Experimental Basis for Intravenous Vaccine Therapy in Chronic Arthritis with a Summary of Results Obtained in Patients, Ann. Int. Med. **5**:1447 (June) 1932. (*q*) Lichtman, S. S., and Gross, L.: Streptococci in the Blood in Rheumatic Fever, Rheumatoid Arthritis and Other Diseases, Arch. Int. Med. **49**:1078 (June) 1932. (*r*) Coste, F., and Forestier, J.: Streptocoque et rhumatisme chronique, Presse méd. **40**:1589 (Oct. 22) 1932. (*s*) Ashworth, O. O.: Bacteriology and Treatment of Rheumatoid Arthritis, Virginia M. Monthly **59**:452 (Nov.) 1932.

present report summarizes the results of 232 such cultures of synovial fluid and tissue made during the past three years.

Rheumatoid arthritis is represented in this series by 55 cultures, and Still's disease by 2; thus 57 cultures were made of synovial fluid and tissue of patients suffering from so-called chronic multiple infectious arthritis. The remaining 175 cultures may be considered as controls for the cases of arthritis; the great majority were derived from more or less chronic conditions of the joints, both infectious and noninfectious, such as chronic osteo-arthritis, effusions into the knee joint secondary to direct injuries or to tears of the semilunar cartilage, tuberculosis of the joint, gonorrheal infection of the joint, conditions diagnosed as syphilitic involvement of the joints and other miscellaneous conditions of the joints with effusions that were definitely not the result of rheumatoid arthritis.

In classifying the various conditions of the joints, the clinical histories were studied carefully, and all available diagnostic criteria were considered. The patients in the group with rheumatoid arthritis presented the typical syndrome of a chronic polyarthritis, which tended to progress to ankylosis and deformity. Many patients presented the fusiform fingers often found in this disease. The ages of the majority of the persons of this group varied between 10 and 40 years. All degrees of severity of the disease are included in the series. The patients in the group with osteo-arthritis were older (all but three of the forty-two patients being over 40 years of age); hypertrophic changes were demonstrable roentgenographically; no complete ankylosis of the joint (usually the knee) was present; motion was frequently painful, and crepitation could often be detected. All of the tuberculous joints were proved to be of a tuberculous nature by inoculation of guinea-pigs, by culture of synovial fluid or tissue,[4] or by histologic examination of material removed from a joint at operation. The clinical diagnosis of gonorrheal infection of a joint was confirmed by gonococcus fixation tests on the synovial fluid and, in some cases, by isolation of the specific organism. Confirmation of the clinical diagnoses of the various other conditions of the joints was derived from roentgenographic, operative or pathologic examination.

TECHNIC

At the beginning of the work a variety of culture mediums was used. These included beef heart infusion containing dextrose, or dextrose plus ascitic fluid, and infusion of human placenta to which was added dextrose or dextrose and calcium carbonate. In addition, Bacto-brain-heart infusion was employed, as it had given good results in routine cultures. The various special mediums appeared to have

4. Blair, J. E., and Hallman, F. A.: Diagnosis of Surgical Tuberculosis: Comparison of Diagnosis by Inoculation of Guinea-Pigs and by Culture, Arch. Surg. **27**:178 (July) 1933.

no particular advantage over the Bacto-brain-heart infusion, and the latter medium was finally used exclusively. It was prepared according to the prescribed directions, and sterilized in the autoclave at from 15 to 18 pounds' (6.8 to 8.1 Kg.) pressure for twenty minutes. The final p_H was from 7.2 to 7.4. For a solid medium, 2 per cent of flaked agar was added. For subcultures, this infusion medium was used alone, or with the addition of human or rabbit blood.

When possible, specimens were cultured soon after they were obtained, although some of the specimens were not received from the clinic until the next day. Aerobic and anaerobic cultures of broth and agar were made of each specimen; for the anaerobic cultures Buchner tubes were employed.

The cultures were examined daily for visible growth for the first week, then at intervals of about a week for a total period of six weeks. At the end of this time, gram-stained smears from each tube were examined before the tubes were discarded. When cultures were found to be positive, they were immediately subcultured. The subcultures were examined daily for growth, and second subcultures were made from these after five days, whether or not visible growth was present.

RESULTS

Rheumatoid Arthritis.—In this group, 55 cultures were made of material from forty-four patients. Forty-seven synovial fluids, five lymph glands, two synovial membranes and one subcutaneous nodule were cultured. All but two of the synovial fluids were obtained from knee joints; one was aspirated from a wrist joint and one from an ankle joint. Of the 55 cultures, 41 (74.5 per cent) remained sterile throughout the entire period of observation; these included cultures of thirty-seven synovial fluids, two lymph glands, one subcutaneous nodule and one synovial membrane.

In 14 cultures (25.4 per cent) micro-organisms were obtained after periods of incubation varying from one to four weeks. These 14 cultures represented ten synovial fluids, three lymph glands and one synovial membrane. The specimens yielding positive cultures were obtained from a group of persons in whom the duration of arthritic symptoms ranged from a few months to fifteen years.

The organisms obtained in these cultures were: streptococci, three (including two indifferent strains and one unidentified streptococcus); diphtheroid bacilli, two; gram-positive cocci occurring in pairs or short chains, six; gram-positive coccoid bacillus and a gram-negative bacillus, two; a gram-positive coccus and a large gram-negative bacillus, one. The streptococci and diphtheroid bacilli usually were cultured without much difficulty. However, in the other cultures, while the cocci mentioned were found in smears of the sediment after prolonged incubation, it was usually impossible to obtain satisfactory growth even after repeated attempts to subculture.

Still's Disease.—One synovial fluid from a patient with Still's disease remained sterile. One lymph gland from another patient with the same disease gave a growth of gram-positive diplococci which were never successfully subcultured.

Organisms Occurring in Cultures from Synovial Fluid and from Tissues

Chronic Multiple Arthritis	Total Number Cultures	Sterile	Positive	Organisms Isolated	Comment
Rheumatoid arthritis	55	41 (74.5%)	14 (25.4%)	3 Streptococci { 2 inert; 1 unidentified	From synovial fluid and synovial tissue of same patient
				2 Diphtheroid bacilli	From synovial fluid
				6 Gram-positive cocci	From synovial fluids
				2 Gram-positive cocci and gram-negative bacillus	From synovial fluids (3); from lymph glands (3)
				1 Gram-positive coccus and large gram-negative bacillus	From synovial fluids, both from same patient at interval of 1 month (synovial tissue, 1 month after second aspiration, sterile)
				1 Gram-positive diplococcus	From synovial fluid (3 other fluids from same patient sterile)
Still's disease	2	1	1		From axillary gland. The sterile culture was from synovial fluid
Total	57	42 (73.6%)	15 (26.3%)		
Controls					
Osteo-arthritis	42	35 (83.3%)	7 (16.6%)	2 Streptococci, unidentified; 2 Diphtheroid bacilli; 1 Staph. aureus; 2 Gram-positive cocci	All from synovial fluid
Synovitis	45	38	7	3 Streptococci, inert; 2 Diphtheroid bacilli; 1 Staph. aureus; 1 Gram-positive coccus	
Miscellaneous effusions of joints	17	17	0		
Tuberculous joints	14	10	4	2 Mycobacterium tuberculosis*; 1 Staph. aureus and diphtheroid; 1 Gram-positive coccus	
Gonorrheal infection of joints	15	10	5	5 Diplococcus gonorrhoeae	
Joints with syphilitic involvement	14	11	3	1 Diphtheroid bacillus; 1 Gram-positive coccus; 1 Small gram-negative bacillus	
Miscellaneous fluids and tissues	28	21	7	3 Staph. aureus	From fluids of bursae
				2 Streptococci { 1 inert; 1 unidentified	From inguinal gland, adenitis
					From cervical gland, tuberculous adenitis
				1 Gram-positive diplococcus	From hematoma of knee
				1 Mixed culture: Staph. aureus; Escherichia coli; gram-positive diplococcus	From cyst of popliteal space
Total	175	142 (81.1%)	33 (18.8%)		

* It should be emphasized that these cultures were obtained on routine culture mediums, in contrast to the special mediums usually employed for the isolation of tubercle bacilli.

Controls.—Excluding the cultures from the group with rheumatoid arthritis and with Still's disease, and considering the remaining 175 cultures as a group of controls, we found that 142 (81.1 per cent) were sterile and 33 (18.8 per cent) were positive. As indicated, these cultures were made of material from patients with a variety of more or less chronic infectious and noninfectious conditions of the joints.

The micro-organisms occurring in these cultures are varied in kind (table). They include Staphylococcus aureus, streptococci, gram-positive cocci incapable of growth on subculture, diphtheroid bacilli and occasional gram-negative bacilli. Thus there is no particular difference, in this series, between the micro-organisms isolated from either synovial fluids or tissues of patients with rheumatoid arthritis or from specimens obtained in a group with wholly unrelated conditions of the joints. No organism which could be interpreted as possessing etiologic significance was obtained consistently in the group with rheumatoid arthritis. The organisms isolated in this group all have their counterparts in the control group. In addition, among the positive cultures of the control group were found a few staphylococci and also gonococci and tubercle bacilli.

It is of interest to record that in the fifteen cases of gonorrheal arthritis, the 5 positive cultures were all pure cultures of Diplococcus gonorrhoeae; all of these cultures grew readily on the routine medium which we employed. Two pure cultures of tubercle bacilli were obtained in the series of fluids from tuberculous joints cultured on the routine medium. These cultures were visible as small colonies at the bottom of the tubes of broth after six weeks of incubation. In a previous report [4] we have recorded the isolation of tubercle bacilli in a large percentage of cultures from fluids and tissues of tuberculous joints, using special culture mediums. However, the occurrence of cultures of tubercle bacilli on the routine medium appears to be worthy of mention.

COMMENT

A question arises as to the significance of the organisms which have been isolated by various investigators in cultures of synovial fluids and tissues from cases of rheumatoid arthritis and in cultures from cases which served as controls. As stated, the postive cultures which have been obtained represent a variety of bacteria, including streptococci, staphylococci, diphtheroid bacilli and occasionally other organisms. All of these bacteria have been isolated, not only in cases of rheumatoid arthritis, but frequently also in the wholly unrelated conditions of the joints which served as controls. Furthermore, the reports of various groups of laboratory workers have been conflicting as to both the kind and the number of micro-organisms obtained. Considered from the point of view of etiology, a brief survey of recent papers dealing with

the bacteriology of rheumatoid arthritis is sufficient to demonstrate that at present a convincing consistency of results has not been obtained.

Reviews of the bacteriologic work done during the past few years in regard to the etiology of rheumatoid arthritis may be found in several of the recent contributions, e.g., that of Jordan.[5] A critical review of the results which have been obtained is not within the province of this report. However, it may be mentioned that several conditions of the joints are included in some of the reports, without distinction as to clinical diagnosis, thus detracting from any significance which might otherwise be attached to the results. The culture mediums and the technic employed vary considerably, and in some cases the methods used are not described. These and other factors render an evaluation of the results extremely difficult. It is evident, however, that a multiplicity of micro-organisms has been obtained from synovial fluids and tissues in both rheumatoid arthritis and entirely unrelated conditions of the joints.

From a study of the varied bacteriologic results recorded, it is obvious that any one of several interpretations may reasonably be given. It is possible that all of the organisms isolated may be capable of inciting changes in the joint characteristic of rheumatoid arthritis, or none may be of etiologic significance, all being present fortuitously as invaders of the diseased joint. The suggestion has been offered that certain of the streptococci isolated may be laboratory contaminations.[3j, m] Dawson, Olmstead and Boots[3m] reported the isolation on two occasions of Streptococcus viridans from sterile agar subjected to the several manipulations involved in the technic of the Cecil blood culture. Cecil maintains that he has never recovered a streptococcus on repeated exposure of plates to the air of the laboratory.[2] We also have exposed plates to the air of the laboratory, and to that of the operating room during operations, and we have not encountered colonies of streptococci on such plates.

Having obtained streptococci in over 60 per cent of cultures from the blood and joints in cases of rheumatoid arthritis, Cecil, Nicholls and Stainsby "have set forth the proposition that rheumatoid arthritis is a streptococcal infection." Crowe,[3e] on the other hand, expressed the belief that the etiologic agent of rheumatoid arthritis is a staphylococcus, to which he has given the name Micrococcus deformans. It is obvious that these or any other results must have more or less general confirmation to be convincing.

It is true that streptococci have frequently been isolated from the blood or joints of persons with rheumatoid arthritis, but it should be pointed out that the same organisms have not infrequently been obtained

5. Jordan, E. P.: The Microbic Etiology of Rheumatic Fever and Arthritis, Arch. Path. **10**:79 (July) 1930.

in control cultures. Furthermore, in some laboratories all varieties of streptococci, as well as other micro-organisms, have been isolated, but no consistency of results has occurred, even under supposedly uniform working conditions. The lack of corroborative results of any one report becomes more manifest with each addition to the already long list of bacteriologic reports. The one exception has been cited.

Jordan [5] suggested that there are two explanations compatible with the repeated isolation of various streptococci: "that arthritis can be caused by streptococci of many types, not specific, or that the streptococcus of arthritis has many inconstant features. The doctrine of microbic dissociation, as developed by Hadley and others may serve as the ultimate explanation for such apparent inconsistency." It would appear that dissociation deserves careful consideration from this point of view. The literature contains numerous isolated observations of variations of streptococci from the normal, all of which, when considered together, indicate that the phenomenon of dissociation may have been in operation. We have repeatedly observed varying degrees of pleomorphism in cultures of streptococci, and forms closely resembling cocci in cultures of diphtheroid bacilli; these observations are undoubtedly not uncommon in other laboratories. A relationship between diphtheroid bacilli and streptococci has been demonstrated by Mellon [6] and by Ramsin and Givkovitch.[7] The transformation of one to the other form has been reported by Koch and Mellon,[8] Straus [3o] and Cooley.[9] In view of these observations it would seem that the frequent isolation of diphtheroid bacilli from cases of chronic arthritis should receive consideration. It is by no means to be assumed that every diphtheroid bacillus so isolated represents a dissociated streptococcus. However, a careful study of the possibility of these relationships in rheumatoid arthritis seems to be desirable. Information thus obtained would be of service in evaluating the claims which have been made regarding the rôle of streptococci in this disease. Even if diphtheroid bacilli obtained from cases of rheumatoid arthritis should be shown to be closely related to the streptococci from these sources, the problem still remains of explaining the inconstancy of their isolation and their occurrence in some control cultures.

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6. Mellon, R. R.: Studies in Microbic Heredity: V. The Biogenetic Law of Haeckel and the Origin of Heterogeneity Within Pure Lines of Bacteria, J. Bact. **11**:203 (March) 1926.

7. Ramsin, K., and Givkovitch, M.: Transformations du streptocoque hémolytique, Compt, rend. Soc. de biol. **95**:952 (Oct. 29) 1926.

8. Koch, R., and Mellon, R. R.: The Biological and Clinical Significance of Diphtheroids in the Blood Stream, J. Bact. **19**:25 (Jan.) 1930.

9. Cooley, L. E.: Dissociation of Streptococci, J. Infect. Dis. **50**:358 (April) 1932.

In the development of the hypothesis that streptococci play an etiologic rôle in rheumatoid arthritis, considerable emphasis has been placed on the frequent occurrence in this disease of the so-called foci of infection, from which streptococci may often be isolated. While cultures of various foci yield streptococci in a large number of cases, it should be remembered that other bacteria may also be isolated from these foci, notably staphylococci and diphtheroid bacilli. The latter organisms cannot be ignored if foci are assumed to be the source of infection in rheumatoid arthritis. Furthermore, many adults who show no indications of rheumatoid arthritis harbor these same organisms in similar foci. Certain constitutional and environmental factors, of course, may play a contributory rôle in the development of the disease.

If rheumatoid arthritis is of infectious nature, it would seem that a disproportionately large number of synovial fluids yield sterile cultures. Since the course of the disease is protracted, it has been assumed that the organisms originally inciting the disease processes are gradually destroyed or removed by the defense mechanisms of the body. As pointed out by Margolis and Dorsey, in their series the average duration of the symptoms was a matter of months or years, and absolute quiescence of the process was a prerequisite for the reconstructive operations which supplied material for their cultures. They assumed that the few positive cultures obtained represented organisms which "retained their viability despite the natural reparative processes which had been exerted by the affected tissues over periods of months or years." [31] On the other hand, the conviction has been voiced by other investigators that it would be difficult to conceive of streptococci which possessed sufficient vitality to remain in or about affected joints for such long periods.[31]

Until evidence to the contrary is offered it appears reasonable to assume that rheumatoid arthritis is caused by no one specific etiologic agent, either infectious or noninfectious. It must be assumed that in many cases numerous factors are at work. Undoubtedly there are cases of rheumatoid arthritis in which the onset was the result of infection, although the specific organism cannot be identified. The hypothesis of the relation of allergy to rheumatic fever, which has been developed by Swift and his co-workers,[10] Zinsser [11] and others, may reasonably be applied also to rheumatoid arthritis. Experimental attack on the relation of allergy to arthritis has been made by Freiberg [12] and deserves to be carried further.

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10. Swift, H. F.: Rheumatic Fever, J. A. M. A. **92**:2071 (June 22) 1929.

11. Zinsser, H., and Yu, H.: The Bacteriology of Rheumatic Fever and the Allergic Hypothesis, Arch. Int. Med. **42**:301 (Aug.) 1928.

12. Freiberg, J. A.: Allergy as a Factor in the Production of Proliferative Arthritis, Arch. Surg. **18**:645 (Feb.) 1929.

SUMMARY AND CONCLUSIONS

1. In a series of 57 cultures of synovial fluids and tissues from chronic multiple arthritis (55 from rheumatoid arthritis and 2 from Still's disease), a total of 41 (74.5 per cent) remained sterile and 14 (25.4 per cent) yielded positive cultures. The micro-organisms obtained in the positive cultures included streptococci, diphtheroid bacilli, gram-positive cocci incapable of growth on subculture and an occasional gram-negative bacillus associated with the aforementioned bacteria.

2. In a series of 175 cultures of synovial fluids and tissues from a variety of chronic infectious and noninfectious conditions of the joint other than rheumatoid arthritis, 142 (81.1 per cent) were sterile and 33 (18.8 per cent) were positive. The positive cultures included Staphylococcus aureus, indifferent streptococci, gram-positive cocci incapable of growth on subculture and diphtheroid bacilli.

3. No direct etiologic significance is attached to any of the organisms obtained in this series.

4. It is felt that at the present time no specific bacteriologic agent may be considered to have been demonstrated as the etiologic cause of rheumatoid arthritis, particularly in view of the multiplicity of results and the lack of general confirmation of any one report.

CLINICAL CONSIDERATION OF THE ETIOLOGY OF PEPTIC ULCER

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Benign duodenal, gastric and anastomotic ulcers are usually referred to as peptic ulcers because they are invariably to be found in regions subjected to the bathing influence of the acid chyme and because it is assumed that the eroding action of the gastric juice is of paramount significance in their development. There are still many factors regarding the etiology, course and chronicity of the lesions which remain imperfectly understood. Even a cursory review of the literature on the subject is convincing evidence of the complexity of the problem. It is my purpose here to review briefly a few of the more important hypotheses advanced to explain the genesis and the course of peptic ulcer. I shall attempt also to arrange the various hypotheses so as to make them apply in a practical manner to the problem of ulcer in man.

HYPOTHESES CONCERNING THE CAUSE OF PEPTIC ULCER

Circulatory Disturbances.—Virchow [1] was under the impression that disturbance of the veins and the arterioles of the submucosa finally resulted in localized necrosis of the muscularis and the mucous membrane. The peptic action of the acid gastric chyme would then cause the ulceration. Hauser [2] and, more recently, Eggers [3] suggested that hemorrhagic infarcts are the immediate pathologic processes that eventually result in necrosis of the gastro-intestinal mucosa. W. J. Mayo [4] described an anemic spot on the anterior surface of the duodenum. He expressed the belief that this area might be increasingly vulnerable to the development of ulceration because of circulatory

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1. Virchow, Rudolph: Historisches, kritisches und positives zur Lehre der Unterleibsaffektionen, Virchows Arch. f. path. Anat. **5**:281, 1853.

2. Hauser, G.: Die peptischen Schädigungen des Magens, des Duodenums und der Speiseröhre und das peptische postoperative Jejunalgeschwür, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, part 1, p. 339.

3. Eggers, H.: Gastritis und konstitutionelle Innervations- und Zirkulationsstörungen, Deutsche med. Wchnschr. **55**:957 (June 7) 1929.

4. Mayo, W. J.: Pathologic Data Obtained from Ulcers Excised from the Anterior Wall of the Duodenum, Ann. Surg. **57**:691 (May) 1913.

deficiency. Reeves [5] noted poor vascularization of the first portion of the duodenum and the pyloric portion of the lesser curvature, and suggested that in consequence of this there was localized ischemia with increasing vulnerability of the tissues to vascular insults. Wilkie [6] mentioned that the factor of chronicity might well be related to the impoverished vascularization of the pylorus and the first portion of the duodenum. Reeves noted attenuation of the speed of the blood current as it traverses the small arteries of the mucosa, thus, he felt, rendering the areas particularly liable to local embolism and thrombosis. Payr [7] tied off large vessels to the stomach; occasionally this resulted in acute ulceration in the areas supplied by the vessels. He found that the introduction of a dilute solution of formaldehyde into a small gastric artery would often result in chronic and even in perforating gastric ulcers. He found that the lumen of the infected vessels had been greatly narrowed by this procedure, the blood supply to localized areas within the wall of the stomach thus being decreased. Gallagher [8] was able to produce acute ulcers in the duodenum by rendering the localized areas anemic for thirty minutes by means of clamping the mucosa.

Erosion of Tissue by Acid.—Sippy,[9] Bolton,[10] Hurst and Stewart,[11] Morton [12] and, more recently, Mann,[13] Dragstedt,[14] Matthews [15] and

5. Reeves, T. B.: A Study of the Arteries Supplying the Stomach and Duodenum and Their Relation to Ulcer, Surg., Gynec. & Obst. **30**:374 (April) 1920.

6. Wilkie, D. P. D.: The Blood Supply of the Duodenum with Special Reference to the Supraduodenal Artery, Surg., Gynec. & Obst. **13**:399 (Oct.) 1911.

7. Payr, Erwin: Experimente über Magenveränderungen als Folge von Thrombose und Embolie im Pfortadergebiete, Arch. f. klin. Chir. **84**:799, 1907.

8. Gallagher, W. J.: Acute Traumatic Ulcers of the Small Intestine; Observations on the Effects of Application of Clamps on the Gastro-Intestinal Tract: An Experimental Study, Arch. Surg. **15**:689 (Nov.) 1927.

9. Sippy, B. W.: Gastric and Duodenal Ulcer: Medical Cure by an Efficient Removal of Gastric Juice Corrosion, J. A. M. A. **64**:1625 (May 15) 1915.

10. Bolton, Charles: Ulcer of the Stomach, London, Edward Arnold & Co., 1913.

11. Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcer, New York, Oxford University Press, 1929.

12. Morton, C. B.: Observations on Peptic Ulcer: I. A Method of Producing Chronic Gastric Ulcer; a Consideration of Etiology, Ann. Surg. **85**:207 (Feb.) 1927.

13. Mann, F. C.: The Chemical and Mechanical Factors in Experimentally Produced Peptic Ulcer, S. Clin. North America **5**:753 (June) 1925.

14. Dragstedt, L. R.: Contributions to the Physiology of the Stomach: XXXVIII. Gastric Juice in Duodenal and Gastric Ulcers, J. A. M. A. **68**:330 (Feb. 3) 1917.

15. Matthews, W. B.: Production of Intestinal Ulcers by Active Gastric Juice, Proc. Soc. Exper. Biol. & Med. **28**:960, 1931.

many others pointed out the part played by the eroding action of abnormally acid gastric juice in the production and the persistence of peptic ulceration. Hurst and Stewart noted that the lesions were confined to the portions of the stomach and the duodenum that are habitually bathed with acid chyme. Moszkowicz [16] assumed that hyperacidity of the gastric secretion injures the wall of the stomach in the region of the fundic glands, particularly in the region of the lesser curvature, and that the wall of the intestine is likewise susceptible to similar trauma, whereas within the stomach the portion including the pyloric glands seems to be partly protected. With Silbermann [17] and Büchner,[18] Moszkowicz assumed that psychically stimulated gastric juice is the cause of erosions of the mucosa.

Neurogenic Factor.—Von Bergmann [19] and many other observers considered that derangement of the nervous system was the most significant single factor in the causation of peptic ulceration. Some derangement of the function of the sympathetic and parasympathetic nervous system is considered by advocates of this hypothesis to result eventually in localized spasmophilia of the duodenal or gastric musculature, with consequent areas of mucosal or submucosal ischemia. In consequence, there is a diminished resistance in the localized areas which results eventually in erosion of the mucosa. The prolonged continuation of this nervous irritability tends to the production of chronic ulcer. Singer,[20] more specifically, defined hyperirritability or actual neuritis of the vagus nerve as the cause of peptic ulcer. Hartzell [21] showed that section of the vagus nerve definitely decreases, at least for a time, the acidity of gastric secretion.

It might thus be postulated that the increase in the activity of the vagus nerve brought about by increasing the rate of secretion of the gastric acids tends to increase the incidence of ulcer. Beaver and Mann [22] showed that dissection of the vagus nerves of the stomach prevents the occurrence of ulcers in some instances following certain opera-

16. Moszkowicz, Ludwig: Ueber die Entstehung der Magengeschwürkrankheit (Gastropathie), Klin. Wchnschr. **9**:385 (March 1) 1930.

17. Silbermann, I. S.: Experimentelle Magen-Duodenalulcuserzeugung durch Scheinfüttern nach Pawlow, Zentralbl. f. Chir. **54**:2385 (Sept. 11) 1927.

18. Büchner, Franz: Magensaft, Gastritis und peptisches Geschwür, Klin. Wchnschr. **9**:1, 1930.

19. von Bergmann, G.: Ulcus duodeni und vegetatives Nervensystem, Berl. klin. Wchnschr. **50**:2374, 1913.

20. Singer, Gustav: Peptisches Geschwür—Lungentuberkulose—anatomische Vaguserkrankung, Arch. f. Verdauungskr. **43**:410 (March) 1928.

21. Hartzell, J. B.: The Effect of Section of the Vagus Nerves on Gastric Acidity, Am. J. Physiol. **91**:161 (Dec.) 1929.

22. Beaver, M. D., and Mann, F. C.: The Production of Peptic Ulcer After Section of Gastric Nerve, Ann. Surg. **94**:1116 (Dec.) 1931.

tions which would otherwise tend to produce ulcers. Cushing [23] was of the opinion that irritative disturbance of either fiber tracts or vagal centers in the brain stem is responsible for ulcer in certain instances.

Inflammation and Infection.—Konjetzny,[24] Orator and Metzler [25] and Puhl,[26] among others, have stated their belief that duodenal and gastric ulcers are the results of inflammatory processes, with destruction of tissues, which begin at the surface of the mucous membrane and from there gradually spread into the depths of the tissues. They are of the opinion that the lesions never develop in healthy mucosa, but always as a result of gastritis or duodenitis. Lebert [27] and Cohn [28] injected pus intravenously into experimental animals and produced acute lesions in the stomach and duodenum, thus adding to the evidence that infection is a cause of ulcer. Letulle [29] injected streptococci and staphylococci intravenously into animals and was able to produce acute ulcer of the stomach. Bezançon and Griffon [30] produced acute gastric ulcers after the experimental intravenous injection of pneumococci. Turck [31] produced round ulcers of the stomach and duodenum in dogs after feeding them colon bacilli over a prolonged period. In 1913, by intravenous injection of streptococci of the proper grade of virulence, Rosenow [32] produced ulcer of the stomach and the duodenum in animals; he believed that the ulcers were due to a localized infection and a secondary digestion of the gastric mucosa. He later advanced the hypothesis that the usual form of gastroduodenal ulcer may be due to

23. Cushing, H.: Peptic Ulcers and the Interbrain, Surg., Gynec. & Obst. **55**:1 (July) 1932.

24. Konjetzny, G. E.: Die chronische Gastritis des Ulcusmagens (zur Beurteilung der Operationsanzeigen und der Operationserfolge beim Magen-Duodenalgeschwür), Zentralbl. f. Chir. **50**:1026 (June 30) 1923.

25. Orator, V., and Metzler, F.: Klinische und experimentelle Beiträge zur Ulcusfrage: III. Zur Frage der Pathogenese und malignen Entartung des Magen-Duodenalgeschwürs, Deutsche Ztschr. f. Chir. **202**:167 (May) 1927.

26. Puhl, E.: Ueber die Entstehung und Entwicklung des Magen-Duodenal-Geschwürs, Arch. f. klin. Chir. **158**:1, 1930.

27. Lebert, quoted by Rosenow, E. C.: The Causation of Gastric and Duodenal Ulcer by Streptococci, J. Infect. Dis. **19**:333 (Sept.) 1916.

28. Cohn, B.: Klinik der embolischen Gefässkrankheiten mit besonderer Rücksicht auf die ärztliche Praxis, Berlin, A. Hirschwald, 1860, vol. 16, p. 696.

29. Letulle, Maurice: Origine infectieuse de certains ulcères simples de l'estomac ou de duodénum, Bull. et mém. Soc. méd. d. hôp. de Paris **5**:360 (Aug. 10) 1888.

30. Bezançon, F., and Griffon, F.: Ulcérations gastriques au cours de la septicémie pneumococcique chez le cobaye, Bull. et mém. Soc. anat. de Paris **74**:409 (May) 1899.

31. Turck, F. B.: Further Observations on the Etiology and Pathology of Peptic Ulcer, Brit. M. J. **1**:922 (April 20) 1907.

32. Rosenow, E. C.: The Production of Ulcer of the Stomach by the Injection of Streptococci, J. A. M. A. **61**:1947 (Nov. 29) 1913.

localized infection by streptococci having a special elective affinity for the mucous membrane of the stomach and the duodenum. In 1924, he [33] reported the isolation, from excised ulcers and from foci of infection in patients suffering from peptic ulcer, of streptococci which had a selective affinity for the stomach and duodenum when they were injected intravenously into animals and which in many instances produced hemorrhage and ulceration. Further evidence corroborating the impressions of Rosenow was adduced by Meisser,[34] who produced chronic foci of infection in dogs by devitalizing some of their teeth and making injections into them of streptococci obtained from the infected teeth of patients suffering from ulcer of the stomach. Hemorrhage or ulceration of the gastroduodenal mucosa was produced in many of these dogs.

Evidence to support the foregoing hypotheses is supplied by the multiplicity of ways in which ulcers have been produced experimentally. In most instances, the experiments resulted in the production of acute ulcers or mucosal erosions which had a tendency to heal rapidly and which, as a rule, did not have the general characteristics of ulcers in man. Mann and Williamson [35] described a method for producing in animals a chronic ulcer which was similar in most respects histologically to peptic ulcer in man. They drained the duodenal secretions, as well as the bile and pancreatic juice, into the terminal part of the ileum and then transplanted loops of jejunum or ileum into the position usually occupied by the duodenum. Following this procedure, subacute ulcer usually developed beyond the pylorus in the jejunal mucosa just distal to the line of suture. Mann and Williamson believed that the chemical action of the acid chyme, which was undiluted by duodenal content, on the jejunal mucous membrane was the cause of the ulceration, and that the mechanical factor of impingement of the acid chyme on the jejunum, through the pylorus, had an effect in producing the lesions and in particular, perhaps, in determining the site of the ulcers.

Matthews and Dragstedt [36] added corroboration of the factor of acid erosion as a cause in the production of ulcer. They adduced evidence by various operative procedures on animals to suggest that the chemical action of pepsin-hydrochloric acid, particularly in concentration

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33. Rosenow, E. C.: Experimental and Clinical Studies on Focal Infection and Elective Localization; Newer Findings and Their Significance, J. Am. Dent. A. **11**:963 (Oct.) 1924; Dental Sum. **44**:954 (Nov.); 1026 (Dec.) 1924.

34. Meisser, J. G.: Further Studies on Elective Localization of Bacteria from Infected Teeth, J. Am. Dent. A. **12**:554 (May) 1925.

35. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409 (April) 1923.

36. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **55**:265 (Sept.) 1932.

in pure, undiluted gastric juice, can by itself produce typical chronic progressive ulcers in the stomach, duodenum, jejunum, ileum or colon. They reproduced experimentally a counterpart of the ulcer of Meckel's diverticulum in man by implanting a small isolated pouch of gastric wall into the jejunum and ileum. This resulted in progressive ulcers in the jejunum in 85 per cent of the experiments, and when the isolated pouch was implanted into the ileum, in 100 per cent. The result was cited as a remarkable example of the susceptibility of an organism's living tissue to the irritating action of pure, undiluted gastric juice. Mann and Bollman [37] also demonstrated a definite gradient in susceptibility to ulcer of the duodenum, jejunum and ileum, suggesting that the ileum is much more sensitive to the formation of ulcer than the part of the bowel ordinarily accustomed to receiving the acid chyme.

A similar gradient in susceptibility was suggested by Harper,[38] who attached a piece of ileum to an isolated gastric pouch and produced ulcer in practically all experiments. He performed the same operation by using strips of duodenum, and found that the upper part of the small bowel was much more resistant to the acid-eroding action of the gastric pouches, and that ulcers occurred much less frequently. Experimental work thus gives conclusive evidence that the eroding action of undiluted gastric juice is undoubtedly one of the chief factors in the production of chronic ulcer. No hypothesis for the formation of peptic ulcer in man can possibly omit the consideration of these pertinent observations. It is extremely doubtful, however, that it will become possible to place the sole responsibility for the genesis of ulcer and its subsequent behavior through the life cycle on this single cause.

ULCER DIATHESIS

Many investigators have observed that certain persons are particularly liable to the development of peptic ulcer; this has led to the postulation that there must be some definite anatomic or physiologic abnormality which increases the susceptibility of these persons to the development of ulcer. Draper [39] stated that certain anthropometric relations as well as certain psychologic factors are characteristic of the ulcer-bearing patient, and he referred to these measurable components as "the ulcer constitution." Similar observations were made

37. Mann, F. C., and Bollman, J. L.: Experimentally Produced Peptic Ulcer; Development and Treatment, J. A. M. A. **99**:1576 (Nov. 5) 1932.

38. Harper, F. R.: Development of Experimental Peptic Ulcer; Changes in Acidity and Treatment, Proc. Staff Meet. Mayo Clin. **7**:318 (June 1) 1932.

39. Draper, George; Dunn, H. L., and Seegal, David: Studies in Human Constitution: I. Clinical Anthropometry, J. A. M. A. **82**:431 (Feb. 9) 1924.

by Stenbuck,[40] who expressed the belief that there is something characteristic in the appearance of the patients. Their faces are usually thin and drawn, with high malar prominences; they are poorly nourished and energetic in demeanor, and present an anxious expression. Other observers believe that a "vasoneurotic diathesis" is the required condition preceding the development of peptic ulcer.

Müller and Heimberger [41] examined fresh specimens with a capillary microscope immediately following partial gastrectomy. They found spasm and atony of the arterioles, capillaries and venules of the gastric mucous membrane. They intimated that they could also demonstrate similar vascular abnormalities in the mucous membrane of the lips and in the skin of their patient. They assumed that this diathesis was the result of congenital or acquired disharmony in the structure and the function of the peripheral blood vessels.

Hurst and Stewart described hypersthenic gastric diathesis and intimated that it is an inborn variation from the average normal which manifests itself in a short stomach accompanied by active peristalsis and rapid evacuation, and in hyperchlorhydria with gastric hypersecretion. Although they admitted that the condition is compatible with the perfect function of the digestive organs, they expressed the belief that it is one of the essential predisposing factors in the production of duodenal ulcer. They stated that persons with long stomachs, if exposed to the exciting causes of ulceration, are likely to have gastric rather than duodenal ulcers.

VARIOUS HYPOTHESES IN THE PROBLEM OF ULCER IN MAN

In reviewing the various hypotheses advanced by physiologists to explain the genesis of ulcer, it must be mentioned that the hypotheses usually represent successful efforts in the production of ulcer in experimental animals. No doubt much valuable information is thus acquired, but it is difficult to condense and correlate it into the problem of ulcer in man. Confusion soon results when an attempt is made to apply a specific single cause for ulcer to the heterogenous clinical complexities of the behavior of the syndrome initiated by ulcer in man.

In all probability, the picture puzzle of ulcer will be satisfactorily conjoined only by the application and the correlation of the combined knowledge accumulated by physiologists, pathologists, surgeons and clinicians. When the information obtained by physiologists withstands the critical analysis of clinicians and is practical in its application to the

40. Stenbuck, J. B.: A Description of the Type of Facies Found in Cases of Ulcer of the Stomach and Duodenum, Am. J. Surg. **38**:181 (Aug.) 1924.

41. Müller, Otfried, and Heimberger, Hermann: Ueber die Entstehung des runden Magengeschwürs, Deutsche Ztschr. f. Chir. **187**:33 (Aug.) 1924.

diverse problems of ulcer in man, and when clinical facts can be taken by the physiologist and correlated with experience in the laboratory, the disjointed segments of the puzzle of peptic ulcer will have been approximated to the ultimate solution of this most important problem.

A careful analysis of the causes assigned for the formation of ulcer reveals that many are not at all applicable to the problem of ulcer in man, and that others apply only in a limited degree. I have attempted to rearrange certain of the important hypotheses concerning the formation of ulcer into a clinical classification which seems applicable to the problem in man. Peptic ulcer is probably the result not of a single factor but of several interacting factors; these will be considered separately. The factors can best be summarized under three heads: (1) the factor of trauma to tissue, (2) the factor of aggression and defense and (3) systemic factors.

Factor of Trauma to Tissue.—Under this heading can be considered all the traumatizing influences which cause or accompany the original aberration from its normal state in the mucous membrane or in the wall of the viscus. There may be involvement from the mucosa downward. There may be disturbances in the submucosal tissue, which by virtue of its consequent loss of resisting potentiality will the more readily disintegrate and succumb to the eroding process. Various experimenters have amply demonstrated that there are numerous ways in which this can be brought about. One illustration presents itself in the work of Rosenow, who postulated septic emboli settling as tiny nests in the depths of the tissue, progressing there into bundles of inflammatory islands, destroying the resistance of the local tissue and thus leading to ulceration. Other locally active factors can readily be supplied by vascular spasm, local spasmophilia of the muscles, irritating substances which are ingested and cause mucosal injury, and various other mechanical and chemical processes through which injury to the tissue may occur. Frequently gastric ulcers arise in association with foreign bodies, such as bezoars. Furthermore, ulcers are rather common complications arising in conjunction with diaphragmatic hernia at the point of maximal mucosal irritation. They present good examples of the ulcers arising mainly from local trauma to tissues. Single insults to tissue from whatever cause undoubtedly can produce disturbances which may cause symptoms and serious complications. No doubt hemorrhage or even perforation can be the result of single attacks on gastro-intestinal tissue. Chronic ulcer, however, is rarely the result solely of such trauma. The acute lesions heal rapidly unless some perpetuating factor of persisting injury to tissue comes into play.

Areal inflammatory lesions, mucosal erosions and acute ulcers probably can result from local insult to tissue, but they most likely

represent only one of the causes, or one of the stages, of chronic ulcer. For the completed accomplishment of chronic ulcer they need assistance from other factors which keep the original lesions from healing.

Factor of Aggression and Defense.—The only common denominator which is consistently and readily applicable to the lesions is that they occur in tissues bathed by the acid gastric chyme. When tissues other than those naturally accustomed to the chemical and mechanical action of gastric juice are exposed to the aggression of the acid chyme, the potentiality for ulceration promptly develops. Obviously, certain factors must arise which change either the resistance of the tissues to the eroding action of the peptic juice or the nature of the chyme so as to heighten its eroding potentialities. It is also evident that the change of balance is not permanent or invariably active in the same degree, because alternation of healing and activity is one of the inherent characteristics of the lesions. In many instances the ulcerating process terminates spontaneously, leaving only a scar to bear witness to the fact that anything unusual has occurred in the area. During the usual normal physiologic cycle the factors of aggression included in the eroding potentialities of the acid gastric chyme are amply counteracted by gastroduodenal tissues which satisfactorily protect themselves against this digestive action. So long as the balance between the defense of tissue and the aggression of acid chyme is properly maintained, nothing unusual happens. If one tips the scales, however, by heightening for a considerable period the factor of aggression or destroys in some way the mechanism of defense, it is conceivable that erosion of tissue will take place. Physiologists have amply demonstrated the increased vulnerability of tissues to the eroding action of the gastric chyme which has greatly accentuated acid-pepsin values. The more successful they are in obtaining acid chyme free from intragastric or extragastric diluents, the surer they are of producing erosions and ulcers in tissue exposed to these juices. They have furthermore demonstrated that tissues unaccustomed in their normal physiologic existence to the eroding actions of the acid chyme will succumb more surely and quickly.

The resistance of the jejunum, ileum and colon to the chemical action of undiluted gastric juice decreases progressively from the jejunum to the colon. It is of significance that factors of aggression which in themselves are inadequate to produce ulcers when tissues are naturally protected are capable of producing ulcers in tissues not usually so protected.

If trauma were caused by infected emboli, vascular spasm or mechanical irritation of the tissue which, normally is amply resistant to the acid factor of aggression, or if these eroding potentialities were intensified for a considerable period by oversecretion or underdilution, the physiologic requirement for the development of ulcer would seem

to be completed. Certainly these factors would produce ulcer in animals, and there is no reason to assume that any other result would obtain in man. These factors of aggression and resistance are applicable in the case of esophageal ulcer; with increased vulnerability of tissue, as by the infection and the regurgitation of acid chyme, erosion may easily occur there. Similarly, the peptic ulcers occurring about heterotopic gastric tissues, such as are occasionally demonstrable in the vicinity of Meckel's diverticulum, are practically always found in contiguous regions that are called on to resist the full aggression and irritation of the secretory products of these tissues. Since the tissues are not intended by nature to counteract the aggression of these secretory irritants, they seem to succumb more easily to chemical insults of this type.

Systemic Factor.—It is possible to produce in experimental animals physiochemical abnormalities which can readily be applied to the problem of peptic ulcer in man. Substantial corroborative evidence of the importance of the two factors just considered are available from experimental laboratories. There are, however, certain biologic phenomena to which man alone is heir. It has been observed that during periods in which the general health of patients has been undermined, the liability to development or recurrence of peptic ulcer seems to be appreciably accentuated. Frequently, with improvement in general health, there is less difficulty in controlling the symptoms, and the ulcer progresses rapidly to a quiescent state. In reviewing the histories of patients with peptic ulcer, it is not uncommon to find that the origin of symptoms occurred during periods of diminished resistance, and frequently the patients have noted that periods of reactivation correspond exactly to periods during which they were in the throes of some acute infection. The application of a yardstick to measure physical characteristics in the patients prone to the development of ulcer has not been very successful, because the factor of greatest importance seems to be one which is more psychophysiologic than physical and which can be measured anatomically and physically with great difficulty. Moreover, this factor seems to be fluctuating rather than constant. The syndrome of ulcer is characterized by periodicity and intermittency, and many chronic ulcers advance to complete cicatrization and healing; obviously, therefore, the factors which are at one time capable of producing and activating the lesions finally may cease to exert their influence and allow the ulcer to go on to quiescence or even to complete and permanent healing.

The characteristics so often duplicated in cases of peptic ulcer seem especially noticeable in cases of duodenal or anastomotic ulcer. There is a striking uniformity of temperament, but even more striking is the

similarity of mental and nervous reactions. Whether to consider these responses physiologic or psychologic seems of no great ultimate importance, since the two types are inseparable and in the end are probably cause and effect in reversible possibilities. The behavior and reactions of the patients are similar, and they conduct their affairs with like dispatch. They are unusually alert, attentive and keen, and frequently appear a bit stimulated, often resembling patients with moderate hyperthyroidism. They are ambitious, intensive, driving and high-strung. They are usually introspective, sanguine, suspicious, sensitive and given to periods of worry and depression. They are persistent in their activities, relentless in the pursuit of their objectives and forgetful of their physical requirements when they are busy with their occupational routine. They are likely to carry on despite obstacles until nervously and physically exhausted. Because of their persistence and ambition, they are frequently successful in their activities. They are, as a rule, willing to accept unusual responsibilities and often live persistently in an environment conducive to the development of great mental tension. The liability for the development of peptic ulcer among persons who live rather intensive lives is suggested by the incidence of the lesions in a series of two hundred specialists in medicine. Almost 20 per cent of the specialists were found to have peptic ulcers, practically all of which were duodenal; at least an additional 20 per cent admitted taking alkalis at intervals, especially during periods when they were unusually busy and overworked, in an attempt to keep up with their usual activities. These facts become increasingly interesting and significant in comparing the incidence of ulcer in this group with the incidence among two hundred Negroes living in a county-seat in central Texas. Negroes of all types were deliberately chosen for this group; most of them, of course, still represented the slow-moving, easy-going type, untouched by aspiration for culture. No instance of ulcer complicated by perforation, obstruction or hemorrhage was encountered. In only one instance was there sufficient evidence in the history to make a diagnosis of peptic ulcer. Incidentally, this instance occurred in a fretful, nervous, worrying Negro whose wife confided that he was constantly worrying about himself, taking medicine and complaining. Three per cent of the entire group had indigestion which was intensified late after meals, but in no other way did the history suggest the presence of peptic ulcer. Each Negro was questioned regarding his work, education, responsibilities, food and habits. In most instances, the actual living conditions were investigated. The diet of the Negroes was not balanced, and their habits almost invariably included the abuse of tobacco and alcohol. They dissipated recklessly. Their hours of sleep were entirely without regularity. They ate whenever they could and whatever they could get, and they lived under pathetic hygienic conditions; yet the syndrome

of chronic peptic ulcer was encountered rarely among them. They were to a great extent without work, and although many of them, even those with large families, scarcely knew the source of the next day's food, they usually seemed surprisingly unconcerned and laughed and jested about their difficulties.

The intricacy of modern life, with its ever-increasing rapidity of progress, exacts a toll in the health of those who choose to run in its race. Throughout the various strata of society there has always existed a certain sprinkling of persons who possess characteristics which are often reduplicated by patients having the syndrome of peptic ulcer. There seems to be a slightly greater tendency to find them among the better educated, more ambitious and more intensive members of society. Their abilities and their willingness to accept responsibility naturally increase the complexity of their lives far beyond that of those who follow along unperturbedly so long as others guarantee a more or less comfortable existence. Occasionally, there will arise in the life of a person, regardless of his position in society, troubles and periods of nervous or physical exhaustion during which he may be more liable to the development of peptic ulcer. Ordinarily his wants are limited, and his life is relatively simple. During the last decade, however, standards, especially in America, changed. Opportunity went recklessly about, knocking at every one's door. Success, as measured in terms of acquired wealth, was everywhere in evidence. American business crowded to the limit the resourcefulness of those connected with it. Increasing speed and efficiency became the American motto. Modern inventions came to the assistance of those who demanded more time-saving devices. Competitive requirements became more intricate, and better, keener and more intensive methods were necessary for those who sought to succeed. All America became prosperous. Barbers, butlers and ditch-diggers rubbed elbows with financiers in the offices of their brokers. Unfortunately, all this speed and hurry and recklessness developed a momentum and a pace which eventually was bound to produce a nation of nervously and physically exhausted persons. Then came the catastrophic behavior of the stock market, the period of precipitous deflation and the economic depression, and promptly a period developed in which there was much maladjustment. In the wake of all this intoxicating orgy were many persons for whom it became an actual struggle to survive. It is not difficult to understand that such a decade might well produce the heightened susceptibility of an increased number of persons to diseases which can be influenced by nervous and mental trauma.

Curiously enough, the desirable virtues of the modern, intensive, aggressive American, the characteristics which have been eulogized and designated as the cardinal marks of American successes, are precisely

the characteristics so often reduplicated in the ulcerous type of patient. Because a premium is paid for these characteristics, an ever-increasing number of persons will acquire them. Consequently, one may expect an increase in diseases having their origin in deranged nervous systems, and undoubtedly peptic ulcer is one of these diseases.

The periodicity and intermittency of symptoms in cases of ulcer frequently are determined by the variability of psychophysiologic influences incident to daily experiences of the patient. During periods of great emotional strain and of prolonged and unrelieved worry, and during long periods of mental or physical fatigue or of strain subsequent to catastrophies of any sort, symptoms are likely to originate or to reestablish themselves.

The rapidity with which epigastric pain with characteristics of peptic ulcer develops following an unexpected catastrophe is often remarkable. It has been a consistent experience of physicians treating ulcer that it is most difficult to accomplish the cessation of the manifestations of the lesion if patients continue working under tension or if they are constantly disturbed, worried and restless while under a regimen for ulcer in a hospital.

It has been pointed out that occasionally patients who present a syndrome suggestive of peptic ulcer do not have peptic ulcers.[42] These patients are of the same type as those who are likely to have ulcer. Furthermore, it has been shown that just as symptoms of ulcer frequently reestablish themselves during periods of stress, so is the pseudo-syndrome also likely to arise under similar psychophysiologic disturbances. There is further similarity in the analogy in that, just as in cases of uncomplicated peptic ulcer the symptoms usually become readily controllable when the patient ceases active work, evades responsibility and takes a vacation, so also does the pseudo-ulcer syndrome usually disappear promptly even with the prospect of a pleasant holiday.

The pertinent analogy between these syndromes and the type of patients who experience them and their general behavior extending into the minutest details of symptoms suggests that the disturbance which is at the root of the entire syndrome is identical in both instances, and that this crucial derangement is in the nervous system. Factors which seem capable of influencing periodic reactivation of ulcer, which can prevent the healing of ulcerous lesions and which at times are entirely capable of bringing forth symptoms mimicking the apparent ulcer syndrome, although there are no demonstrable lesions detectable on exposed gastroduodenal tissues, must be of pertinent significance in the cause of the syndromes. The variability of the degree and of the intensity

42. Rivers, A. B., and Vanzant, F. R.: Peptic Ulcer Syndrome Without Ulcer, Nebraska M. J. **17**:465 (Nov.) 1932.

of these psychophysiologic tendencies probably represents the fluctuant which determines whether or not and when the syndromes will arise.

It is conceivable that, when ulcer is absent or when the defense reactions of the tissue are normally intact, a syndrome similar to that experienced without ulcer and entirely dependent on the disturbed neurogenic factors may develop. With the return of normal nervous reactions the balance is quickly reestablished, and the symptoms disappear. In the event of prolonged persistence of nervous hyperirritability and consequent accentuation of the aggressive factor, or in the presence of increased vulnerability of gastric or duodenal tissues, it is suggested that ulcer may easily be the final result. Quiescence or activity of the ulcer syndrome could be an alternating condition dependent on fluctuating psychophysiology with its resultant mechanical and chemical gastrointestinal alterations. Marked elevation of the acid-pepsin values is often noted during periods of excitement and tension, and it may be that one of the mechanisms of reactivation during these periods is related directly to chemical conditions affected by the nervous system in this manner.

CLINICAL APPLICATIONS OF VARIOUS HYPOTHESES

The three factors which thus stand out prominently from an analysis of various hypotheses applicable to the problem of ulcer in man are: (1) local trauma to tissue, (2) resistance of tissue to the aggression of acid gastric chyme and (3) systemic conditions. But it is not a matter of choosing which of these three includes the most logical causes for the formation of ulcer, because such lesions are probably the result of the combined interaction of the various factors. A graphic representation of these factors lending themselves jointly to the production of a composite picture of ulcer can be effected by the erection of a triangle (fig. 1).

Although each of these factors, as represented in figure 1, may be capable of producing ulcer, it is suggested that an interaction of several or all probably represents the more common formula; furthermore, in all probability the interaction of the various factors probably influences the course of the entire life cycle of the ulcer.

The many factors instrumental in causing peptic ulcer undoubtedly are of varying significance in different cases, and it is probable that the behavior of the lesions is influenced by fluctuations even in the same case. No inflexible and invariable constant will apply to the problem of the cause of ulcer in man; now one factor, now another assumes the position of major importance. It is, therefore, necessary to make an individual problem of each case of peptic ulcer.

Factor of Trauma to Tissue.—There are certain instances in which the trauma to tissues obviously overshadows other factors in etiologic

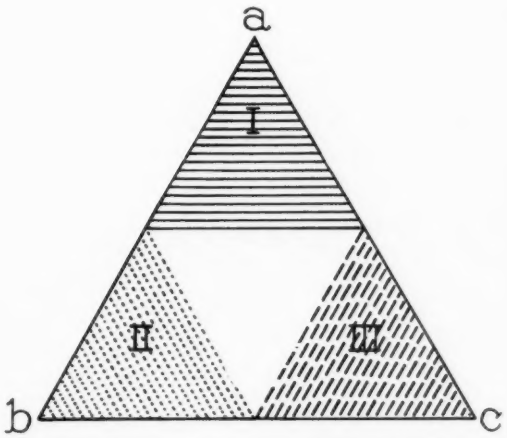

Fig. 1.—Triangle represents a diagrammatic scheme for the completed formula of chronic ulcer. It is constructed of three smaller triangles, indicated as triangles *I*, *II* and *III*. Each of the triangles lends two of its sides and their included angle to the formation of the larger triangle. Triangle *I* represents the factor of trauma to tissue; triangle *II*, the defense against aggression, and triangle *III*, the systemic factor.

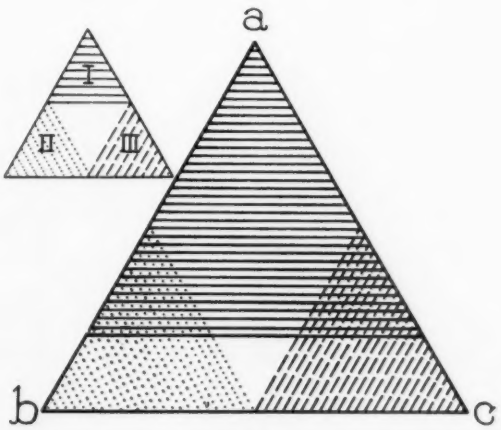

Fig. 2.—The base line of triangle *I* is pushed further into the larger triangle until it occupies almost the entire larger figure. This factor overshadows in importance the several other factors in the production of ulcer.

importance (fig. 2). It is not to be assumed that other factors do not enter to a varying degree into the production of peptic ulcers or into the course of the activity. It is intimated that in certain instances trauma to tissue seems to play a primary part in the onset and the course of the lesions. Such local injury to tissue is illustrated by the following cases:

CASE 1.—A girl, aged 5 years, shortly before coming to the Mayo Clinic, had an attack of acute tonsillitis. Several days after the onset she became weak, vomited large amounts of blood and passed tarry stools. Roentgenograms at the clinic gave evidence of duodenal deformity which was assumed to be due to an ulcer in that region. The infection was probably primarily responsible for the development of the hemorrhage. The tonsils were removed, and there has been no recurrence of the gastro-intestinal hemorrhages.

CASE 2.—A man, aged 34, had indigestion intermittently for ten years. There were six or eight episodes during which he complained of symptoms suggestive of peptic ulcer. With each episode he had hemorrhages, in the form of either melena or hematemesis. Between the attacks he was well. Roentgen investigation showed no evidence of deformity of the stomach or of the duodenum. Operation disclosed a small area of redness surrounded by considerable stippling in the duodenum. A diagnosis of areal duodenitis was made. Two dental roots were taken out, and material from them was injected into animals. In all of the animals hemorrhagic areas developed promptly throughout the upper part of the duodenum and about the pylorus. There has been no recurrence of the hemorrhages. It is assumed that the infection from the roots of the teeth may have been responsible for the inflammatory condition in the duodenum.

CASE 3.—A woman, aged 49, had epigastric pain and vomiting. At intervals during twelve years she complained of indigestion characterized by much vomiting and abdominal distention. Curtailing the amount of food promptly brought about improvement of the symptoms. In the last three or four years she had noted occasionally a burning sensation in the epigastrium, which was relieved by the ingestion of small amounts of food. On a few occasions there had been severe epigastric pain. Occasionally a small amount of blood was noted in the vomitus. Roentgenograms revealed the presence of esophageal diaphragmatic hernia with gastric ulcer; this was confirmed by exploration. The hernia was repaired. Nothing was done to the ulcer because it was assumed that it was due to traumatic erosion of the mucous membrane, the result of marked incarceration and angulation of the stomach in the thorax. The hernia was reduced, and seven months afterward roentgenograms revealed complete healing of the ulcer. It is obvious that local trauma to tissues incident to the presence of the diaphragmatic hernia was responsible for the ulcer.

CASE 4.—A woman, aged 33, presented herself at the clinic because of an abdominal tumor which had been detected two months previously and because she had lost strength and weight. At the time of examination the tumor was about 8 cm. in diameter. It was freely movable and not especially tender. Cramps had developed in the upper part of the abdomen two weeks prior to admission to the clinic. Occasionally there had been nausea and vomiting shortly after meals. Roentgenograms gave evidence of a large ulcer on the lesser curvature of the stomach. Exploration revealed the presence of a gastric ulcer and a large intragastric mass, which consisted of a ball of hair. This was removed. On the assumption that the ulcer was due to trauma from the foreign body, nothing was done to it. The patient recovered uneventfully and has remained well.

These illustrative cases seem to adduce evidence to suggest that local changes in tissue, whether due to infection, mechanical irritations or other trauma, can become in certain instances the chief causes of gastroduodenal lesions. This does not mean that other factors, such as the eroding action of peptic juice, do not in some way contribute to the ulcerating process. It suggests, however, that in the absence of such trauma the lesions would probably not have developed (fig. 3).

PREDOMINANCE OF FACTOR OF DEFENSE OF TISSUES AGAINST AGGRESSION OF ACID

Careful evaluation of the available data occasionally suggests that in aggression of acid and defense of tissue lies the chief cause of peptic ulcer and of the maintenance of its chronicity. Physiologists seem to have demonstrated experimentally that this factor alone can

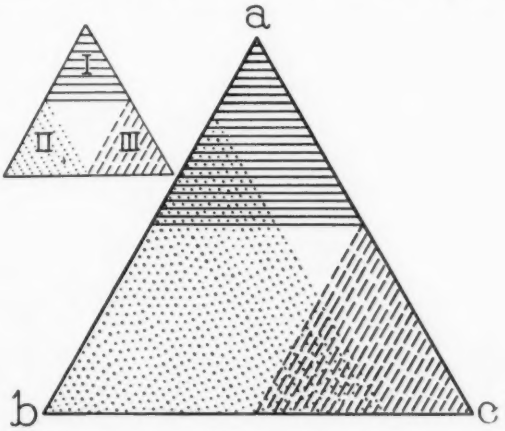

Fig. 3.—Diagrammatic representation of the predominance of the factor of defense against aggression of acid in the causation of ulcer. Triangle *II* has shifted its base line to include the major portion of triangle *abc*.

adequately accomplish the formation of chronic ulcer in animals. In certain instances such experiments find analogies in man. Certain patients seem to possess gastric mechanisms which maintain chyme of tremendously high concentration of acid, and pepsin values are often grossly accentuated. Furthermore, these patients frequently sustain high levels of acidity for unusually long periods after various stimulating influences have been applied to the gastric secretory mechanism. Increased liability to the formation of ulcer can readily be assumed in such cases, particularly in the presence of traumatized gastric, duodenal or jejunal tissues. Experiments with animals have further demonstrated that the impinging of highly acid chyme on tissues unaccustomed to the bathing influence of such chyme made them liable to the develop-

ment of ulcer. Similar conditions at times arise in man. The surgeon may have erroneously attached the ileum to the stomach on the assumption that he was making a gastrojejunostomy to cure duodenal ulcer. If the gastro-ileostomy functions satisfactorily, thereby effectively draining the major portion of the acid gastric chyme into the ileum, a gastro-ileac ulcer is almost certain to develop. The increased liability of patients to the development of gastrojejunal ulcers in the presence of retained high gastric acidity following gastro-enterostomy furnishes a further corollary to the experimentally produced chronic ulcers of Mann and Dragstedt. In such instances the factor of aggression as inherent in in the high acid values possesses increased vulnerability because it is impinged on jejunal or ileac tissues which by nature are endowed with

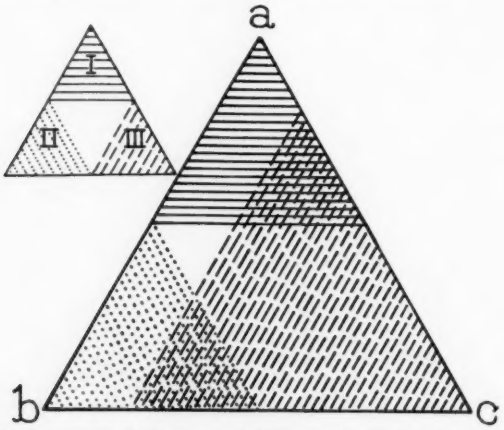

Fig. 4.—Predominance of the systemic influence in the causation of peptic ulcer. In this instance, triangle *III* has shifted its base line until it overshadows the other triangles included in triangle *abc*.

less efficient protecting mechanisms than are shown by the first portion of the duodenum, which is usually able successfully to withstand prolonged trauma by highly acid gastric juice. Case histories illustrating these factors follow:

CASE 5.—A man, aged 46, came to the clinic complaining of indigestion. Characteristics typical of ulcer dated back to childhood. Between the ages of 20 and 35, he had a great deal of difficulty in controlling the symptoms. At the age of 40 and again at 45, the difficulty had increased. Roentgenograms gave evidence of a duodenal deformity which was assumed to be duodenal ulcer. Results of the histamine test gave values as follows: The first specimen showed 106 total acid, 88 free hydrochloric acid, and 1,520 units of pepsin (normally below 500 units); the second specimen, 108 total acid, 94 free hydrochloric acid and 1,520 units of pepsin; a third specimen, 110 total acid, 96 free hydrochloric

acid and 1,680 units of pepsin; a fourth specimen, 126 total acid, 100 free hydrochloric acid and 2,840 units of pepsin; a fifth specimen, 136 total acid, 102 free hydrochloric acid and 2,360 units of pepsin, and a sixth specimen, 148 total acid, 106 free hydrochloric acid and 1,560 units of pepsin. Posterior gastro-enterostomy was performed; three weeks afterward another estimation of the histamine was made; the maximal total acid was 104, and the free hydrochloric acid, 98. Pepsin at this time was estimated to be 2,620 units. Obviously, in this case the factor of greatest potential danger for the reformation of ulcer rests in the tremendous aggression of acid and pepsin.

CASE 6.—A man, aged 24, entered the clinic in the spring of 1932, complaining of indigestion; characteristics typical of ulcer were present. Roentgenograms gave evidence of duodenal deformity, and operation was advised. An ulcer on the anterior wall of the duodenum was excised, one on the posterior wall was cauterized, and a pyloroplasty was made. Shortly afterward there was definite evidence of recurring ulceration beyond the pylorus with the formation of a crater. The estimation of gastric acidity after the use of histamine showed the following values: 86 free hydrochloric acid, 100 total acid; 118 free hydrochloric acid, 92 total acid; 120 free hydrochloric acid, 96 total acid; 104 free hydrochloric acid, 84 total acid; 104 free hydrochloric acid, 82 total acid, and 96 free hydrochloric acid, 74 total acid. Estimation of pepsin made on the specimen with the highest acidity showed 2,700 units. The ulcer on the posterior wall was then excised, and a gastroduodenostomy was made. Two weeks following this, gastric acidity was 104 total, and 98 free hydrochloric acid. In this specimen 1,900 units of pepsin was recovered.

Apparently the greatest problem in prevention of further difficulty in this case would have to be directed toward regulation of gastric chemistry, because the potentiality for the formation of ulcer under these conditions would be very high. The intimate mechanism responsible for the markedly attenuated ferment and acid values noted in cases 5 and 6 cannot be accurately ascertained. I have frequently noted, however, that in cases of peptic ulcers there seems to be a marked tendency for oversecretion of acid and attenuated values for pepsin. Stimulating test meals will often produce sustained curves of elevated values for acid and pepsin for much longer periods when ulcer is not present, and it may be that the instances of formation of ulcer and its maintenance rest with the persistence of the factor of attenuated aggression inherent in the acid pepsin.

CASE 7.—A man, aged 35, presented himself at the clinic because of abdominal pain. One year prior to admission, cholecystectomy was performed, and six months after this, gastro-enterostomy because of a duodenal deformity which was assumed to be ulcer. Shortly afterward, severe abdominal pain had appeared at irregular intervals. Nausea and vomiting followed the ingestion of all types of foods, and frequently acid gastric contents were regurgitated. There were periodic epigastric pain and, frequently, pain in the lower part of the abdomen, often associated with diarrhea. The patient had lost from 20 to 30 pounds (9 to 13.6 Kg.). Roentgenograms revealed the presence of a small ulcer just below the gastro-enteric stoma. Estimation of gastric acidity showed slightly elevated total and free hydrochloric acid. At operation an ulcer was found opposite an anastomosis made between the stomach and the lower part of the ileum.

Experiments on animals disclose that when the lower part of the small bowel is exposed to the traumatizing influence of acid chyme, it is likely to cause ulceration. Apparently the same condition obtains in man. Unfortunately, in this case

the gastro-ileostomy worked so well that most of the gastric content was deposited through the stoma and only a small amount by the pyloric route. It is not surprising that a gastro-ileac ulcer developed in this case.

CASE 8.—A girl, aged 9 years, was brought to the clinic because of intervals of pain in the region of the umbilicus which sometimes radiated to the right or left groin. Dark, tarry stools had been noted at intervals, usually three or four days after the onset of the pains. There was definite evidence of secondary anemia. Estimation of the gastric contents showed values of 40 for total and 24 for free hydrochloric acid. At exploration an ulcer was found at the juncture of the ileum and at Meckel's diverticulum, where the contents of the diverticulum impinged on the ileac wall. Examination of the submucosa of the Meckel's diverticulum revealed the presence of heterotopic gastric tissues.

In discussing ulcer of Meckel's diverticulum, Lindau and Wulff [43] stated that islands of heterotopic gastric mucosa similar histologically to that in the fundus of the stomach have almost invariably been found in these cases. Matthews and Dragstedt reproduced a counterpart of the ulcer of Meckel's diverticulum in animals by implanting a small isolated pouch of gastric wall into the jejunum and the ileum. When the pouch was transplanted into the jejunum, jejunal ulcer developed in 85 per cent of the animals, whereas, when the acid gastric juice was led into the ileum, it developed in 100 per cent.

The daily observation of patients with peptic ulcer soon impresses one with the fact that in certain patients it is particularly difficult to reduce the values of acid and pepsin in the stomach. Whether this is due to a particularly active gastro-intestinal reflex, whether it is due to excessive irritability of the mechanism responsible for the pouring of secretions into the stomach or whether it is due to deficiency of the neutralizing mechanism is difficult to determine. The evaluation of these causative factors, applicable in cases of gastric ulcer, cannot fail to take cognizance of the fact that in these cases the factor of predominant importance seems to be the regulation of gastric chemism. The case histories herein recorded seem to illustrate the predominant significance of these chemical factors. Cure or prevention of further ulceration should include efforts to reduce materially the acid gastric constituent in patients with gastric ulcer.

PREDOMINANCE OF SYSTEMIC FACTORS

There are certain instances in which peptic lesions seem to bear a distinct relationship in their etiology and course to the general health of the patient. Debilitating diseases, such as prostatic disease, and many

43. Lindau, Arvid, and Wulff, Helge: The Peptic Genesis of Gastric and Duodenal Ulcer; Especially in the Light of Ulcers in Meckel's Diverticulum and the Postoperative Ulcers in the Jejunum, Surg., Gynec. & Obst. **53**:621 (Nov.) 1931.

other conditions, are not infrequently associated with peptic ulceration. Periods of general diminished resistance following or during the course of acute or chronic infections not infrequently tend in some way to render the gastroduodenal tissues more susceptible to ulceration or to reactivation of ulceration if it is already present. Patients commonly experience hemorrhages from peptic lesions during the course of an acute infection of the upper part of the respiratory tract. It is not difficult to postulate that under such conditions the local resistance of the gastroduodenal tissues might definitely be diminished. The fluctuating influences dependent on the nervous and mental reactions of the patients seem to be still more important. The increased liability to the development of peptic ulcer when activities are carried on under tremendous tension has been suggested. Careful questioning of patients harboring peptic ulcer frequently brings out the information that it was during periods of psychic disturbances that the syndrome of ulcer began. Often also periods of recurring difficulty are simultaneous with periods during which the patients were particularly worried or were engaged in work requiring unusual nervous tension. In fact, there are many instances in which the entire syndrome of ulcer seems to be related in its inception and termination to disturbances of the nervous system. Often it is extremely difficult to decide whether the reestablishment of symptoms when patients are known to have peptic ulcers is actually due to a reactivation of the ulcer, because the inception and the termination of the symptoms parallel so exactly and so abruptly the particularly disturbing experiences. Illustrative cases follow:

CASE 9.—A man, aged 22, came to the clinic complaining of indigestion. Typical symptoms of ulcer had been present for a year. He had married about fourteen months previously. His father had given him as a wedding gift a business with which he was only slightly acquainted. He had a great deal of worry incident to the business and many responsibilities incident to the state of life into which he had just entered. It was during this period that the symptoms of indigestion developed. Whenever the patient met a difficult situation which caused him considerable concern, indigestion developed. Total gastric acidity was 98, and free hydrochloric acid, 80. A roentgenogram disclosed duodenal ulcer.

CASE 10.—A man, aged 31, entered the clinic complaining of indigestion of three years' duration. He smoked and drank alcohol excessively. A duodenal ulcer was discovered, and gastro-enterostomy was performed. He was well for eighteen months afterward. Then his wife became ill, and he came with her to the clinic. He was much worried about her illness, and gastric symptoms with definite characteristics of ulcer promptly developed. Later his son became ill and died, and the gastric symptoms recurred. During the following year occasional attacks of indigestion were invariably brought on by worry. Reexamination at the clinic revealed the presence of a gastrojejunal ulcer.

CASE 11.—A man, aged 73, came to the clinic because of prostate trouble. On reviewing the history, it was noted that during his youth he had had indigestion for four or five years. Roentgenograms of the upper part of the gastro-

intestinal tract disclosed evidence of an old duodenal scar. Since there had been no indigestion for thirty or forty years, the patient was closely questioned regarding the treatment which had cured the ulcer. He answered that the symptoms seemed to disappear. As a young man he had lived on a farm. He had married in his early twenties, moved to town and for several years conducted a small business with satisfactory financial results. He then decided to prepare himself for the ministry and moved to a larger city to attend school. Shortly afterward, his first child was born. He soon found that he had not saved enough money to live on. He also learned that his theologic course would take much longer than he had planned. This meant that he had to work at night to earn money; his wife also had to help. After another year their second child was born. This increased responsibilities and difficulties materially. During this period of worry and struggle indigestion developed. The symptoms persisted for three or four years. Then, after settling himself in his ministerial activities in a small town, his life became less strenuous, and with the return of better social and financial conditions his gastric symptoms disappeared permanently.

CASE 12.—A man, aged 70, had had various operations to relieve symptoms of peptic ulcer. The fourth operation, in 1922, was partial resection of the stomach. Shortly before, he was greatly disturbed by the illness and death of his wife. During this period he had uncontrollable indigestion, with symptoms suggestive of penetrating peptic ulcer. In the years following the operation he lived at the home of his married daughter. Many unpleasant incidents arose, and his indigestion recurred. Finally, in 1930, at the age of 68, he married a woman much younger than himself; this resulted in further difficulties. After several months he divorced his wife; not, however, before severe signs of recurring gastrointestinal disturbances had developed. At the time of the examination at the clinic an ulcer was found at the anastomosis just distal to the stoma. Under stimulation of histamine on several occasions, titration revealed the presence of total acids ranging between 84 and 96, and free acids ranging between 68 and 80. The content of pepsin in the gastric juice was about five times the normal amount.

This last group of cases suggest the part played by the nervous system in the causation of gastric symptoms. The exact parallelism between psychic trauma with unusual nervous tension and causation or reactivation of symptoms is apparent. In case 11, there had been no symptoms of ulcer for about forty years. The syndrome in this case exactly paralleled a period in the patient's life when he was living under tremendous psychic disturbances. In case 12, as in many of the other cases, it is difficult to ascertain whether the factor of aggression of acid or the neurogenic factor is of greater significance. In all probability, the neurogenic factor is of significance only because it produces other conditions, such as markedly prolonged, persistent attenuation of the high values of acid and pepsin, and for this reason such patients are increasingly vulnerable to the development of peptic ulcer.

SUMMARY

An attempt has been made to apply some of the hypotheses advanced to explain the etiology of peptic ulcer to the clinical problems of ulcer in man. In all probability, peptic ulcer is the result of several interact-

ing and variable factors. Physiologists have demonstrated that the aggressive action of undiluted juice can, by its eroding potentialities, produce ulcer. It produces ulcer the more effectively when it impinges on tissues unaccustomed and unprotected by nature to receive them. It is suggested that this factor of aggression is the more likely to cause ulceration when the resistance of the tissues exposed is in some way lowered by trauma of any kind. Thus, an infected intestinal wall or mucosa injured by mechanical or chemical irritants might well succumb and disintegrate when a membrane with normal protecting mechanism would remain intact. Systemic factors, if conducive to the diminution of the resistance of tissues or if capable of producing prolonged or persistent accentuation of the factor of aggression in the acid chyme, might well increase the liability to the development of ulcer and its recurrence in such cases. There seems no doubt that the factors involved etiologically in the formation of ulcer vary in different subjects at different times. Consequently, every patient presents problems which must be studied carefully. Such study should reveal the particular factor or combination of factors which will obtain in each case, and correction of their factors should be expected to result efficiently when applied in the treatment of ulcer.

ANGINA PECTORIS

SOME CLINICAL CONSIDERATIONS, WITH SPECIAL REFERENCE TO PROGNOSIS

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AND
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The accuracy of studies on the prognosis of angina pectoris depends on two factors. In the first place, errors will naturally occur because of mistaken diagnoses. There are a great many types of distress or pain in the chest that are not anginal in character which are often confused with true angina pectoris. Second, the duration of life after the symptoms have developed will obviously depend on the care that is taken in ascertaining when the disease actually first manifested itself. Frequently patients date the onset at a time when an attack of severe pain in the chest occurred, but on questioning them directly as to the first time that they had this sort of distress, even in a mild form or on walking, one learns that the disease began 1 or more years previously. The duration of life after the onset of the disease would consequently be greater according to the latter than according to the former notation. With this in mind, 141 patients with angina pectoris who have died were studied. In each case the diagnosis was quite certain and one of us had questioned the patients with care as to the exact onset of symptoms.

There have been numerous studies on the prognosis of angina pectoris,[1] and in general they have shown that the duration of life after angina has developed is from 4 to 5 years. An attempt has been made here to investigate certain factors that might influence prognosis, and

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1. (*a*) Mackenzie, James: Angina Pectoris, New York, Oxford University Press, 1923. (*b*) Herrick, James B., and Nuzum, Frank R.: Angina Pectoris: Clinical Experience with Two Hundred Cases, J. A. M. A. **70**:67 (Jan. 12) 1918. (*c*) Kahn, Morris H., and Barsky, Joseph: Angina Pectoris: A Clinical Analysis of Two Hundred Cases, Ann. Int. Med. **2**:401 (Nov.) 1928. (*d*) White, Paul D., and Bland, Edward F.: A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis: A Study of 500 Cases of the Former Condition and of 200 of the Latter, Am. Heart J. **7**:1 (Oct.) 1931.

to appraise their value. The influence of the blood pressure level, sex, age of onset, age at death of parents, electrocardiographic changes and the effect of recovery from an attack of coronary thrombosis were analyzed. Information differentiating these various factors and the rôles that they may play in prognosis is rather meager. This is particularly true with respect to the differences in angina pectoris that occur in the two sexes.

The cases included in this study were selected in the following manner: Only those were included in which the date of death was known. Cases of angina pectoris occurring in young people with rheumatic aortic valvular disease were excluded. Although they have typical attacks of angina and are liable to sudden death, they do not suffer from

TABLE 1.—*Essential Data of One Hundred and Forty-One Cases of Angina Pectoris*

	Men	Women
Sex distribution	111 cases, 78.8%	30 cases, 21.2%
Age at onset	56 years	58.1 years
Range	36 to 71 years	36 to 71 years
Duration of angina	4.6 years	4.5 years
Range	1 month to 23 yrs.	3 months to 13 yrs.
Age at death	60.7 years	62.7 years
Range	41 to 76 years	46 to 74 years
Blood pressure	149.2/89.2	190/102
Range	95/72 to 238/124	140/74 to 244/130
Patients with systolic pressure under 140	46	None
Age at death of parents:		
Male parent	66.4 years	69.4 years
Female parent	64.5 years	67.3 years
Age at death of parents of patients whose angina began before age of 50	66.7 years	61.5 years

disease of the coronary arteries and may live for many years; they form a separate group. Likewise, a few patients were excluded who had attacks precipitated by paroxysmal rapid heart action. Furthermore, patients first seen during an attack of coronary thrombosis were deliberately excluded, although most of them had antecedent angina, because it was felt that a distorted picture would be obtained. If such cases of acute coronary thrombosis with its high immediate mortality were included, the duration of life for angina would be unfavorably and unreasonably weighted. Notwithstanding this, many of the patients with angina considered in this review did subsequently have attacks of coronary thrombosis from which they recovered or to which they succumbed. The purpose of the study was to throw light on the natural progress of true Heberden's angina as it is met with in general practice, and not in the hospital wards. All the patients were seen at the office or in consultation at their homes, and represent a fair index of what occurs in the general population.

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1. (*a*) Mackenzie, James: Angina Pectoris, New York, Oxford University Press, 1923. (*b*) Herrick, James B., and Nuzum, Frank R.: Angina Pectoris: Clinical Experience with Two Hundred Cases, J. A. M. A. **70**:67 (Jan. 12) 1918. (*c*) Kahn, Morris H., and Barsky, Joseph: Angina Pectoris: A Clinical Analysis of Two Hundred Cases, Ann. Int. Med. **2**:401 (Nov.) 1928. (*d*) White, Paul D., and Bland, Edward F.: A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis: A Study of 500 Cases of the Former Condition and of 200 of the Latter, Am. Heart J. **7**:1 (Oct.) 1931.

to appraise their value. The influence of the blood pressure level, sex, age of onset, age at death of parents, electrocardiographic changes and the effect of recovery from an attack of coronary thrombosis were analyzed. Information differentiating these various factors and the rôles that they may play in prognosis is rather meager. This is particularly true with respect to the differences in angina pectoris that occur in the two sexes.

The cases included in this study were selected in the following manner: Only those were included in which the date of death was known. Cases of angina pectoris occurring in young people with rheumatic aortic valvular disease were excluded. Although they have typical attacks of angina and are liable to sudden death, they do not suffer from

TABLE 1.—*Essential Data of One Hundred and Forty-One Cases of Angina Pectoris*

	Men	Women
Sex distribution	111 cases, 78.8%	30 cases, 21.2%
Age at onset	56 years	58.1 years
Range	36 to 71 years	36 to 71 years
Duration of angina	4.6 years	4.5 years
Range	1 month to 23 yrs.	3 months to 13 yrs.
Age at death	60.7 years	62.7 years
Range	41 to 76 years	46 to 74 years
Blood pressure	149.2/89.2	190/102
Range	95/72 to 238/124	140/74 to 244/130
Patients with systolic pressure under 140	46	None
Age at death of parents:		
Male parent	66.4 years	69.4 years
Female parent	64.5 years	67.3 years
Age at death of parents of patients whose angina began before age of 50	66.7 years	61.5 years

disease of the coronary arteries and may live for many years; they form a separate group. Likewise, a few patients were excluded who had attacks precipitated by paroxysmal rapid heart action. Furthermore, patients first seen during an attack of coronary thrombosis were deliberately excluded, although most of them had antecedent angina, because it was felt that a distorted picture would be obtained. If such cases of acute coronary thrombosis with its high immediate mortality were included, the duration of life for angina would be unfavorably and unreasonably weighted. Notwithstanding this, many of the patients with angina considered in this review did subsequently have attacks of coronary thrombosis from which they recovered or to which they succumbed. The purpose of the study was to throw light on the natural progress of true Heberden's angina as it is met with in general practice, and not in the hospital wards. All the patients were seen at the office or in consultation at their homes, and represent a fair index of what occurs in the general population.

Among these 141 patients there were 111 men (78.8 per cent) and 30 women (21.2 per cent). (All the essential data are charted in tables 1, 2 and 3.) The average age of the men at the onset of angina was 56 years and of the women, 58.1 years. For men the range extended from 36 years to 71 years and for women from 36 years to 70 years. The average duration of the symptoms of angina pectoris was 4.6 years in the men and 4.5 years in the women in this series. The shortest duration among the men was 1 month and the longest was 23 years. For the women, the corresponding figures were 3 months and 13 years. The average age at death for the men was 60.7 years, and 62.7 years for the women. The youngest and the oldest of the former were 41 and 76

TABLE 2.—*Blood Pressure Readings of Patients with Angina Pectoris*

	Number of Cases	Blood Pressure	Duration of Angina, Years	Age at Death, Years
Patients with hypertension (men)	47	175 /100.6	4.3	62.4
Patients with normal blood pressure (men)	62	129 / 80.1	5.0	59.1
Onset of angina under age of 50 (men)	22	138.4/ 77.7	7.2	....
Onset of angina over age of 50 (men)	89	151.9/ 92.1	4.0	....
Onset of angina under age of 50 (women)	4	176 /101.5	6.2	....
Onset of angina over age of 50 (women)	26	192.2/102	4.2	....
Duration of angina of over 5 years (men)	35	148.4/ 87.8	...	....
Duration of angina of over 5 years (women)	11	185.3/ 98.1	...	....
Duration of angina of 1 year or less (men)	12	151.4/ 89.6	...	....
Duration of angina of 1 year or less (women)	7	175.1/ 94.7	...	....
Angina at rest	55	161.7/ 95.6	5.6 (life) 2.9 duration of angina at rest	61.6
Cardiac failure during course of angina (men)	15	160.5/ 96.5	5.4	64.6
Cardiac failure during course of angina (women)	6	200.3/103	6.1	61.3
Obesity	72	.....	4.5	59.3
Normal weight	10	.....	6.9	59.0
Normal electrocardiogram	20	145 / 85	5.9	56.3
Negative T_1 or T_1 and T_2 (men)	21	148.5/ 90.7	3.7	59.7
Positive T_1 or T_1 and T_2 (men)	51	146.3/ 88.0	4.9	59.2
Negative T_1 or T_1 and T_2 (women)	6	219.1/120.8	6.3	61.8
Positive T_1 or T_1 and T_2 (women)	5	167.6/ 97.6	6.2	59.8
Prolonged QRS	11	154 / 97.7	5.4	64.0
Prolonged PR	5	159 / 94	4.9	66.0
Low electromotive force	5	154.2/ 80	8.9	64.4

years, and of the latter, 46 and 74, respectively. These extremes are naturally applicable only to this series of cases. Both younger and older persons suffering from angina pectoris are met with in general practice; in fact, one of us treated a man aged 24 for an acute attack of coronary thrombosis who had angina pectoris for a few months preceding the former condition. He is not included here because he survived and is still living.

The blood pressure showed distinct differences in the two sexes, an observation which is not entirely in accord with the view of Kahn and Barsky,[1c] who stated that blood pressure readings were about the same in the two sexes. The average reading for 109 men was systolic, 149.2 millimeters of mercury and diastolic, 89.2 millimeters of mercury. The extremes were 95 systolic and 72 diastolic on the one hand and 238 systolic and 124 diastolic on the other (one patient with a lower systolic

pressure had a diastolic pressure of 150). The average reading for 30 women was systolic 190 and diastolic 102. The extremes were systolic 244 to 140, and diastolic 130 to 74. It follows that women have much more hypertension with angina pectoris than men, the average difference being about 41 mm. for the systolic pressure and 13 mm. for the diastolic. What is of more clinical importance is that, whereas there were 46 men with angina pectoris with systolic pressure readings under 140, there was no woman with such a reading. In fact, there were only 2 with a pressure between 140 and 150; in one of these this reading was obtained during the height of an acute coronary thrombosis, and in the other it was present after an attack of the same nature. We have had occasion to utilize this feature with profit in cases of pain in the chest among women with low blood pressure in whom we suspected angina pectoris and in whom it was subsequently proved not to be present. One should therefore hesitate to make the diagnosis of angina pectoris unassociated with coronary thrombosis for any woman with a low blood pressure, especially for those under 50 years of age.

A comparison was made between patients who had hypertension and those who had normal pressure. In the first group, there were 47 with an average systolic pressure of 175 and a diastolic pressure of 100.6. The average duration of angina was 4.3 years. The average age at which these patients died was 62.4 years. On the other hand, there were 62 men with an average blood pressure of 129 systolic and 80.1 diastolic. The average duration of anginal symptoms was 5 years. The age at death in these patients with low blood pressure was 59.1 years. One may conclude therefore that in men with angina pectoris who have a low blood pressure the disease begins earlier in life, it lasts longer and the age at death is lower than in those with hypertension.

The effect of age at onset was analyzed to see whether there were any differences either in blood pressure or in the prognosis among those in whom the disease developed early in life. Of the 111 men, there were 22 in whom the angina began before the age of 50 years and 89 in whom it began after that age. The average blood pressure in the younger group was 138.4 systolic and 77.7 diastolic. In the older group the readings were: systolic, 151.9, and diastolic, 92.1. The duration of anginal symptoms was 7.2 years in the younger men and 4 years in the older. There were somewhat similar differences in the group of women. Of the 30 women, there were 4 under and 26 over 50 years of age at the time of onset of angina pectoris. The average blood pressure of the younger group was: systolic, 176, and diastolic, 101.5. The corresponding figures for the older group were 192.2 systolic and 102 diastolic. The duration of the disease was 6.2 years in the former and 4.2 years in the latter. It is clear that the younger persons with angina

pectoris, both men and women, have distinctly lower blood pressures, and that the duration of life is from 2 to 3 years longer than in the older.

An attempt was made to detect any distinguishing differences in the blood pressure in the short lived, as contrasted with the long lived, patients with angina pectoris. A group of 12 men and 7 women in whom the duration of angina was 1 year or less was contrasted with a second group of 35 men and 11 women in whom the disease lasted more than 5 years. No significant differences could be made out.

It is always a matter of interest whether attacks of angina occur only on effort or whether they are present even during rest. In fact, it has often been assumed that angina during rest is more ominous than angina on effort. A study was therefore made with this point in mind. There were 42 men and 13 women in whom attacks occurred not only on effort but also with varying frequency while they were at rest. In all the others, attacks were either entirely related to effort or occurred only rarely when the patients were at rest. A comparison of the blood pressure, the average age at onset of anginal symptoms and the average age at death showed no significant differences. The average duration of life after the onset of angina in this group was 5.6 years, which is even greater than for the entire series. The length of life after the anginal attacks began to occur during rest was 2.9 years. In more than half of the cases, attacks during rest appeared practically simultaneously with the onset of the disease. In a recent study by White,[1d] it was found that 23 patients with angina of this severity died within 3 years, but 16 lived more than 7 years. It therefore follows that the duration of life after the onset of the disease is no shorter in cases of angina decubitus than it is in angina of effort.

Probably the most important etiologic factor in angina pectoris is heredity. It is difficult to obtain accurate data in this regard, because it requires knowledge of the diseases from which all the members of the various families suffer, which must be compared with similar data obtained in control cases. The information available in our cases was inadequate to warrant any such study. An analysis was made, however, of the age at death of the parents of the patients who had angina. The age at death of the male parent of the 68 men about whom there were data was 66.4 years and of the female parent, 64.5 years. The average age for the male parent of 12 women was 69.4 years and of the female parent 67.3 years. It is obvious that the age at death of the parents of the women with angina was about 3 years greater than that of the men. It is curious that the mothers of both the men and the women with angina died at an age of 2 to 3 years less than that of the fathers. This is distinctly different from the situation that exists in the general population. Extensive statistics, especially those obtained by insurance companies, show that the average age of women at death is 2 years or

more greater than that of men. The fact that female parents of patients with angina pectoris died at an age from 2 to 3 years less than that of the male parents may be explained if it is supposed that female parents played a larger rôle than male parents in transmitting the defect of vascular vulnerability. If this were not true, one would have to find that the age at death of the female parents would be over 2 years greater rather than 2 years less than that of the male parents. This conception is further validated when an analysis is made of the 22 patients in whom angina began before they were 50 years, for the female parents died at the age of 61.5 years, whereas the male parents died at the age of 66.7 years, a difference of over 5 years. Additional evidence that the hereditary factor is important can be obtained by comparing the age at death of patients with angina whose parents lived to an average age of over 70 with those whose parents lived to an average age of under 60. There were 26 of the former with a parental average age of 76.5 years and an average age at death of the patients of 63.4 years. There were 19 of the latter, with corresponding ages of 52.1 years and 57.8 years. In other words, patients with angina who have long-lived ancestors live 5.6 years longer than those whose parents die at a younger age.

Not infrequently patients with angina pectoris are subjected to tonsillectomy on the basis that a focus of infection is directly or indirectly related to the production of the attacks. It has become the fashion to search for foci of infection and to ascribe to such foci the cause of many diseases. A review was therefore made, patients who had tonsils removed some time during their life being compared with those on whom tonsillectomy had not been performed. There were no significant differences in the blood pressure findings, the average age at onset of angina or the age at death in the two groups. It is therefore unreasonable to remove tonsils either for prevention or for treatment of angina pectoris.

The relation between angina pectoris and cardiac decompensation is of some interest. There is a current teaching that when congestive failure develops in a patient who is having anginal attacks, the attacks disappear. Although this does frequently occur, it is by no means invariable, for in this series there were 5 men and 1 woman in whom attacks were not only present during decompensation, but in some instances were more troublesome. There were 15 men and 6 women who showed physical evidence of congestive heart failure during the course of the angina. In 7 cases decompensation followed in the wake of an attack of coronary thrombosis. Although the number is small, the proportion of men to women (5:2) is distinctly less than for the entire group of cases (4:1). The effect of hypertension in producing congestive failure is suggested in this discrepancy as in other data that follow. The average blood pressure in the 15 men was: systolic, 160.5,

and diastolic, 96.5. The corresponding figures for the 6 women were systolic, 200.3 and diastolic, 103. These figures are distinctly higher than those for the entire group. The average duration of life after the onset of angina was 5.4 years for the men and 6.1 years for the women. The duration of life after decompensation developed was 2.7 years for the former, and 1.3 years for the latter. The age at death of the men was 64.6 years and of the women, 61.3 years. The figures indicate that hypertension makes it more likely that a patient with angina pectoris will have cardiac decompensation, but that the duration of life after the onset of angina will be a year or more longer than for those who do not have decompensation. The age at death of the men in the group was 4 years greater than in the average of the entire series.

The relation between the recovery from an attack of coronary thrombosis and the course of angina pectoris was also analyzed. There were 21 men and 3 women in this series who recovered from an attack of coronary thrombosis. The average age at the time of the first attack of coronary thrombosis for the men was 57.6 years, and for the women, 65 years. The average age at death of the former was 60.8 years and of the latter, 68.6 years. It would seem that the length of life after recovery from an attack of coronary thrombosis was from 3 to 3½ years, and that the women were apt to have such attacks later in life.

Obesity is generally regarded as being related to the development and progress of angina pectoris. A comparison was therefore made between patients with excess weight and those who were normal or underweight. There were 68 men and 14 women, whose weights were known. Of these, there were 60 men with an average excess weight of 26.9 pounds and 12 women with an average excess weight of 46 pounds. The average age at death of the obese group was 59.3 years for the men and 59 years for the women. There were 8 men and only 2 women whose weights were normal or subnormal. The age of these at death was 59 years. Although these data are crude, as the greatest weight was not determined and many patients had lost weight previously, they are in accord with our general impression that obesity is not a significant factor in the production of angina, but rather that it indicates the type of person in whom the disease is more prone to develop. If obesity were actually related to the causation of angina pectoris, one should expect that the obese would die at an earlier age than those who are not overweight. Such was not the case in this study.

In an attempt to throw light on any factor that might influence the prognosis of angina pectoris, the presence or absence of electrocardiographic abnormality naturally deserves consideration. There were 104 patients for whom electrographic tracings were taken. Of this group, 20 showed essentially normal curves. Their average blood pressure

readings were 145 systolic and 85 diastolic. The duration of the angina was 5.9 years and the average age at death was 56.3 years. Thus it would appear that the finding of a normal curve is not necessarily a good prognostic sign, since the age at death of patients with such curves was less than the average age of the entire series and of those having electrocardiographic abnormalities. The duration of the anginal symptoms, however, was about 1 year longer in cases with normal electrocardiograms than the average of the entire series.

The changes that were particularly analyzed were negativity of the T wave in lead I or leads I and II, spread of the QRS complex and initial ventricular complexes of low amplitude. There were 21 men with inversion of the T wave in lead I or leads I and II and 51 men with positive T waves in these leads. The blood pressure readings were practically the same in the two groups. The duration of angina was 3.7 years for those with negative T waves and 4.9 years for those with positive T waves. The age at death, however, was about the same in these two groups, averaging over 59 years. The finding of negative T waves, therefore, shortens the total duration of angina by a little more than 1 year. There were 6 women with negative T waves and 5 with positive T waves. The former group had a much higher blood pressure than the latter. The readings were 219.1 systolic and 120.8 diastolic as compared to 167.6 systolic and 97.6 diastolic. The duration of angina was the same, a little more than 6 years. The average age at death was 61.8 years for the group with negative T waves and 59.8 years for those with positive T waves. In general it may be said that negative T waves in lead I or leads I and II shorten the duration of angina pectoris in men a little more than a year. This finding does not affect the prognosis in women, probably because a negative wave in lead I is so often an accompaniment of hypertension.

In 11 patients with a prolonged QRS complex (0.1 second or more), the average blood pressure was: systolic 154 and diastolic 97.7. The duration of angina was 5.4 years, and the average age at death was 64 years. It is evident that such a finding had no unfavorable influence on the progress of the disease; in fact, the opposite was somewhat indicated. A similar statement can be made for 5 patients who showed distinct prolongation of the PR interval. There were only 5 patients who showed electrocardiograms with distinctly low amplitude of the QRS complexes in all leads. The average blood pressure was 154.2 systolic and 80 diastolic. The duration of angina was 8.9 years and the average age at death was 64.4 years. Here again an electrocardiographic finding that generally carries with it a particularly grave prognosis seemed to have no such significance in this small group, for their duration of life was longer than the average of the entire series. It is difficult to compare these data

with the study by Willius [2] on the prognosis of patients with negative T waves, as in his study the duration of life was not calculated from the onset of symptoms, but rather from the time the patients were first seen by him.

In patients who have angina pectoris, sudden and unexpected death is a frequent occurrence. In fact, when the diagnosis is accurately made, such an event is anticipated. The frequency of sudden death and the other types of fatality and the causes were therefore analyzed in this study. Information was obtained concerning the manner of death of 86 men and 18 women. By the term sudden death is meant that a patient who is doing well, generally ambulatory, and attending to some duties is stricken dead instantly. There were 43 such instances among the men, or 50 per cent, and 5 among the women, or 28 per cent. In addition, there were 26 (30 per cent) men and 7 (39 per cent) women who died of coronary thrombosis. There were 5 men (5.8 per cent)

TABLE 3.—*Causes of Death in One Hundred and Four Cases of Angina Pectoris*

Cause of Death	Males		Females	
	Number	Per Cent	Number	Per Cent
Sudden	43	50	5	28
Coronary thrombosis	26	30	7	39
Congestive heart failure	5	6	2	11
Miscellaneous (acute pulmonary edema, cerebral accidents, bronchopneumonia, cancer, etc.)	12	14	4	22

and 2 women (11.0 per cent) who died of ordinary congestive heart failure. Among the men, 3 died of acute pulmonary edema and 4 of cerebral accident; the latter cases were instances of cerebral hemorrhage or cerebral embolus. The remainder died of miscellaneous causes, such as bronchopneumonia, cancer and similar conditions. It is apparent that about one half of the patients with angina pectoris died suddenly and unexpectedly. No doubt in many of these, coronary thrombosis was the cause of the sudden death. This is not invariably true, however, for we have seen patients of this type who, it was revealed on post-mortem examination, had atheroma of the coronary arteries but no thromboses. Approximately 30 per cent of the patients with angina died after manifesting clinical evidence of coronary thrombosis. Most of the remaining patients died as a result of some form of cardiovascular disease, such as congestive heart failure, acute pulmonary edema and cerebral accidents.

2. Willius, Frederick A.: Electrocardiography and Prognosis, Arch. Int. Med. **27**:434 (Oct.) 1922.

SUMMARY

This study concerns 141 fatal cases of angina pectoris seen in consultation practice. They were selected only so far as the diagnosis was definite and the entire duration of the disease was known. Cases that were first seen during an attack of coronary thrombosis were excluded. The main factors which were studied were those that had some possible bearing on prognosis.

There were 111 men and 30 women, a ratio of approximately 4 : 1. The average age at onset for the men was 56 years and for the women, 58.1 years. The average duration of angina was 4.6 years for the former and 4.5 years for the latter. The extremes were from a few weeks to 23 years. The average age at death was 60.7 years for the men and 62.7 years for the women.

The blood pressure findings were different in the two sexes. The average reading for the men was 149.2 systolic and 89.2 diastolic. The corresponding figures for the women were 190 systolic and 102 diastolic. It is of considerable importance that although there were 46 men with a systolic reading under 140 mm., there were no women with such a reading. The rarity of normal or low blood pressure findings in women with angina pectoris is very helpful in diagnosis.

A comparison of patients with hypertension with those having normal blood pressure showed that in the latter group the disease begins about 4 years earlier and lasts a little longer, and that the age at death is about 3 years less.

In studying the effect of the age at the onset of angina, it was found that in those in whom the disease developed before the age of 50 the duration of life after the onset was 2.3 years longer than in those in whom the disease developed after the age of 50.

No significant differences in the blood pressure could be found in the group of patients who lived less than a year as contrasted with those who lived more than 5 years.

Cases of attacks of angina while the patients were at rest were compared with those in which the attacks occurred almost exclusively on effort. Contrary to expectation, it was found that the duration of life after the onset of the disease, the age at death and the blood pressure readings were not significantly different in the two groups.

Evidence was presented to show that the hereditary factor is of great importance. It was found that those patients whose parents lived to an average age of under 60 died 5.6 years earlier than the group whose parents lived to an average age of over 70. The data also indicated that the defect of vascular vulnerability is transmitted more prominently by the female than by the male parent.

There were no differences in the course of the disease in those patients who had had a tonsillectomy and in those whose tonsils had not been removed.

The relation between angina pectoris and cardiac decompensation was also analyzed. The former frequently did not disappear with the development of the latter. It was found that the presence of hypertension made it more likely that congestive failure would develop some time during the course of the angina. The duration of life, however, after the onset of angina, was a year longer in those in whom decompensation was present than in those in whom it was not. The great frequency of hypertension in women explains the more common occurrence of cardiac decompensation in this sex.

The effect of recovering from an attack of coronary thrombosis was considered. The length of life after such an attack was about 3.5 years in both sexes, but women developed such attacks 3.6 years later in life than men.

Obesity was not found to affect either the age at onset or the duration of the disease. We feel that obesity has no important direct relationship to angina pectoris but merely reflects the constitutional type that is more prone to the disease.

Of 104 patients for whom electrocardiograms were taken, 20 showed essentially normal curves. The duration of the disease was a year longer, but the patients died at an earlier age than did either the average of the entire series or those with abnormal tracings. The duration of life after the onset of angina was 1 year less in those with inverted T waves in lead I or leads I and II than in those without such changes. In a small number of instances showing other electrocardiographic changes, such as prolongation of the PR interval and QRS complex or QRS curves of distinctly low amplitude, the prognosis as to the duration of life was slightly better than for the entire series.

Approximately 50 per cent of the patients died suddenly. In addition, about 30 per cent died of coronary thrombosis. Many of the instant deaths in the former group no doubt were due to coronary thrombosis as well. Somewhat less than 10 per cent died of congestive heart failure. The remainder died of miscellaneous causes, such as cerebral hemorrhage, bronchopneumonia, cancer and similar conditions.

RELAPSES IN CHRONIC ULCERATIVE COLITIS

CAUSES AND PREVENTION

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The cyclic nature of biologic phenomena is by no means confined to normal physiologic processes. The occurrence of cycles in pathologic states is well illustrated by the tendency to remissions and exacerbations which is a characteristic of chronic ulcerative colitis. The joy of the patient and the enthusiasm of the physician at the successful treatment and termination of an attack must always be tempered by the sober realization that the condition may recur. Knowledge of the pathologic changes that take place in this disease leads to a clear understanding of the inherent tendency to recurrence. This analytic study was undertaken in an effort to throw light on the factors which determine the incidence of, or which actually precipitate, the exacerbations, with the hope that the knowledge thus gained will prove valuable in prophylaxis during the quiescent stage or during the period in which the disease is under control. Our attention has frequently been directed to the similarity between factors which initiate the first attack of this type of colitis and those associated with subsequent exacerbations of the disease.[1]

The histories of 364 consecutive patients with chronic ulcerative colitis who registered at the Mayo Clinic in 1931 and 1932 were studied. Many of the patients had been observed at the clinic previously, so that detailed clinical notes of many years were available. In addition, a well organized system of correspondence afforded further information as to clinical progress after dismissal of the patients. Communications were received from almost all of the patients twice yearly, and in most cases more often. The nature of the study would, of course, exclude patients whose disease was continuous—of unremitting activity—and a few other patients in whose records insufficient data were available.

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* The work for this paper was done at the Mayo Foundation when the author was a special student in medicine.

1. Larson, L. M.: Predisposing Factors in the Etiology of Chronic Ulcerative Colitis, Proc. Staff Meet., Mayo Clin. **6**:241 (April 22) 1931.

In 232 cases there were sufficient data to warrant inclusion of the cases in this survey; 209 patients had received medical treatment, and 23 had been previously subjected to some type of short-circuiting operation on the bowel. In every case, diagnostic procedures included proctoscopy, cultures of stools, repeated examinations of stools for pathogenic bacteria and parasites, and roentgenologic study of the thorax and colon; the barium sulphate enema was omitted in the rare case in which it was contraindicated by marked rectal stricture.

The results of the analysis of 209 cases in which treatment had been medical form the basis of this report. Several points of interest concerning the cases in which surgical operation had been performed are also considered.

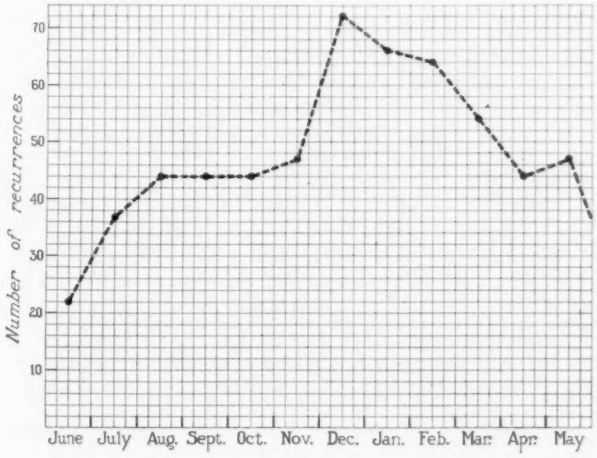
Concerning 276 of the recurrences involving 140 patients definite statements were available relative to the factor which immediately preceded or actually coincided with the beginning of the attack. Under the heading "infections of the upper part of the respiratory tract," which comprise 57 per cent of the total number of recurrences, are grouped colds, influenza, acute tonsillitis, sore throat and pneumonia. In the occasional case, respiratory infections ushered in each relapse. Overexertion occurred in 19 instances (6.9 per cent), and nervous strain in 17 instances (6.2 per cent); specifically, these factors were manifested by fatigue, worry and emotional upset.

An appreciable number of relapses (12 per cent) were associated with conditions which traumatized or increased the irritability of the gastro-intestinal tract. These can be divided into the following classifications: dietary indiscretions, 14 instances (5.1 per cent); epidemic diarrhea, 10 instances (3.6 per cent), and intestinal trauma, 9 instances (3.3 per cent). The dietary indiscretions included overeating of foods high in roughage and gas-forming elements, alcoholism and excess in drinking of water during hot weather. Epidemic diarrhea, the drastic use of cathartics and various forms of manipulation of the bowel, such as proctoscopic examination and administration of barium enemas, irrigations with caustic solution and rectal surgical operations, accounted for the remainder of the attacks in this group.

In an attempt to eradicate every focus of infection, removal of infected tonsils and teeth had been common in the treatment of the patients, both at the clinic and elsewhere. A mild intestinal reaction, subsiding in from two to five days, was a common sequel, but in 14 cases (5.1 per cent) the operation initiated a prolonged recurrence of the ulcerative colitis.

In view of the fact that immunization, active or passive, or both, against diplostreptococcus of chronic ulcerative colitis was carried out

as a routine in the treatment of the patients, an infrequent cause of reactivation of quiescent colitis was the subcutaneous injection of sensitized vaccine. Nine episodes of this sort (3.3 per cent) occurred in 5 patients. The complete absence of recurrences following the use of the concentrated serum (antibody globulin solution) led to an investigation of the circumstances under which the vaccine had been given, since the former is used only at the Mayo Clinic, whereas the latter is given to each patient for administration by the family physician after dismissal. The exacerbation always occurred before the fourth injection of vaccine and usually following the first injection. Overdoses were common; 2 patients apparently became hypersensitive even to minute concentrations of the organism. In only 1 case did a relapse occur following an injection of vaccine at the clinic.



Monthly incidence of 586 recurrences.

Recurrence after abdominal operations were rare in this series. The 4 examples (1.3 per cent) were secondary to appendectomy. Instances in which patients had undergone from one to three major operations during periods of remission without ill effect only to have a severe exacerbation of the colitis initiated by removal of the tonsils or teeth were noteworthy.

In the miscellaneous group of 23 recurrences (8.2 per cent), 4 were associated with allergic manifestations; 3 were caused by attacks of hay fever, and 1 by sensitivity to ingested chicken meat. It is possible, of course, that allergic reactions enter into the etiology of recurrences more frequently than our histories would indicate. Some of the women with quiescent colitis went through pregnancy, delivery and the puerperium without unfavorable incident. In only 1 case did the gravid

state predispose to a return of symptoms; two successive pregnancies were thus complicated. Many women had noted increased intestinal activity and discomfort during the premenstrual phase. The remaining 17 relapses were preceded by acute exacerbations of chronic arthritis, severe bodily injuries, measles, chorea, erysipelas, dermatitis venenata or vaccination for smallpox.

An interesting fluctuation in the monthly incidence of relapses can be noted in the chart. Frequency of relapse was lowest in the summer months, and coincident with the increase in respiratory infections reached its peak in December, January and February. Of 586 exacerbations, involving 209 patients, 202 occurred in the winter, 102 in the summer, 146 in the spring and 136 in the autumn. In the individual case there was often a tendency for attacks to take place during the same month or season annually. In recurrences in the summer, although infections

TABLE 1.—*Relation of Age to Incidence of Recurrence in 165 Cases*

Decade of Life	Cases	Total Duration of Disease, Years	Number of Recurrences	Average*
10–19	16	87.5	60	0.69
20–29	51	256.0	157	0.61
30–39	51	311.5	155	0.50
40–49	24	172.0	74	0.43
50–59	18	126.0	50	0.40
60–69	5	34.0	14	0.41

* Average recurrences per year for each case.

of the upper part of the respiratory tract assumed lesser importance, dietary indiscretions (especially excessive intake of water), epidemic diarrhea and various other types of injury to the bowel represented almost half of the precipitating factors. The comparatively low incidence in summer in the entire series suggested a special study of cases from the southern states. Here the reverse finding was apparent, with the relapses in summer exceeding those in winter, but the relation between the season and the etiologic agent was analogous to that of the entire series. However, since the number of cases from southern states corresponded closely to the general geographic distribution of patients coming to the clinic, they were too few to warrant definite conclusions.

Table 1 includes data bearing on the correlation between the age of the patient and the frequency of recurrences. Only the cases in which definite and reliable information was obtained concerning both the total duration of the disease and the total number of distinct exacerbations after periods of quiescence were included. It will be seen that the frequency in the 165 cases decreased with each decade of life, so that in

the same period of time the patient of more than 40 years of age was likely to have only three-fifths as many relapses as the patient of less than 20 years. Chronic ulcerative colitis beginning when a patient is elderly runs a milder course. As one might suspect, the importance of the various precipitating factors for the different age groups fluctuated in an interesting way: During childhood and adolescence the part played by infections of the upper part of the respiratory tract was paramount, whereas during the third and fourth decades, the recurrences secondary to nervous strain, emotional shock, overexertion and dietary indiscretions increased markedly in frequency. The incidence of attacks was approximately the same for both sexes at various ages.

It might be assumed, on a theoretical basis, that the more extensive the involvement of the colon by the pathologic process, the more frequent would be the number of recurrences. By the use of proctoscopy

TABLE 2.—*Relation of the Extent and the Situation of the Lesion to the Number of Recurrences*

Extent of Lesion*	Cases	Total Duration of Disease, Years	Number of Recurrences	Average†
Rectum and sigmoid	58	312.0	155	0.50
Half of colon‡	30	158.5	83	0.52
Entire colon	56	348.5	185	0.53
Entire colon and terminal portion of ileum	21	168.0	87	0.52

* As determined by roentgenograms and proctoscopic examination.
† Average recurrences per year for each case.
‡ Left half, 25 cases; right half, 5 cases.

and roentgenoscopy of the colon as a routine, it was possible to delineate the situation and boundaries of the lesion in each of the 165 cases in which there were data on the total duration and the total number of attacks. As shown in table 2, the situation and the extent of the disease bore no apparent relation to the incidence of recurrences. No single factor could be considered especially likely to induce reactivation of the process when situated in a particular part of the colon.

The foregoing analysis does not include the 23 cases in which previous treatment had been colostomy, cecostomy, appendicostomy, ileostomy or ileosigmoidostomy. The average interval since the operation was four and four-tenths years. In 21 of the 23 cases, the cyclic attacks of ulcerative colitis had continued with the same precipitating factors, in approximately the same ratio, as in the nonsurgical cases. Second or third operations (plastic repair following colostomy or ileostomy; ileostomy or ileosigmoidostomy in cases in which cecostomy had previously been performed, and subtotal or total colectomy) were performed

on 11 patients of the group. The risk, judging by the mortality rate of the subsequent procedures, was tremendously increased over that of the primary operation. Bargen, Brown and Rankin [2] emphasized the wisdom of confining the operation to the treatment of complications of the disease. Fifteen of the patients had marked stricture of the rectum, extensive polyposis of the colon, vesicosigmoid fistulas or a combination of these conditions. It is clear that even in cases in which treatment is surgical, the problem of recurrence of activity is important and that any guides in the prophylactic care will be valuable.

COMMENT

It may be that the facts elicited in a study of this kind have only relative value. The responsibility for distinguishing between a mild increase in intestinal activity and true exacerbations of the disease rests entirely with the individual investigator. Furthermore, unless he has had the opportunity to trace the patients personally from the inception of the disease through each of the successive exacerbations, with frequent notes on the temperature, body weight, daily number and character of the stools and the degree of anemia, it will be impossible to ascertain the actual duration, or to grade the severity, of the many attacks.

In the care of the patient with chronic ulcerative colitis, one must distinguish between clinical and pathologic activity. Once the disease has appeared, the normal characteristics of the mucous membrane and the other layers of the wall of the bowel are almost invariably permanently altered. Generalized contraction of the lumen is a constant feature, and often a thick-walled, stiff, straight tube remains. Healing of the severe destructive processes may result in the formation of multiple polyps or strictures of the rectum or the colon. With the advent of the first-named complication, the patient may notice, after a period of quiescence, the gradual return of bleeding, tenesmus and the greater frequency of stools. The amount of blood passed is usually out of proportion to the other symptoms. If the second complication develops, pockets of pus may accumulate proximal to the stricture in various parts of the colon, and by sudden discharge over a period of days may simulate a significant increase in pathologic activity.

Rectal stricture, consisting of localized regions of inflammatory tissue and scar tissue on a diffusely narrowed base, will interfere materially with the passage of the normal fecal current, so that the stools are smaller in size and are passed more frequently. Under these conditions,

2. Bargen, J. A.; Brown, P. W., and Rankin, F. W.: Indications for and Technique of Ileostomy in Chronic Ulcerative Colitis, Surg., Gynec. & Obst. **55**: 196 (Aug.) 1932.

therefore, a portion of the patient's difficulties is undoubtedly mechanical, and it is not surprising that approximately a fourth of the patients who were to all intents well continued to have from two to five normal-appearing bowel movements daily over a period of years. Accordingly, in this group we have excluded from consideration as recurrences all exacerbations that did not last at least a month and in relation with which profound changes in the character and the number of the stools were not displayed.

The most important single incitant of recurrences—infections of the upper part of the respiratory tract—accounts for the high percentage of relapses in winter and is unfortunately most difficult to overcome. Although a climate which predisposes to such infections is prone to result in reactivations of the disease, a sojourn in warmer regions is not necessarily effective in preventing them. Apparently the patient carries his susceptibility to colds with him. An attempt to end the episodes by the removal of normal-appearing tonsils or tonsillar tags may be doomed to failure, and, as has been shown, may occasionally result in a severe recrudescence of the colitis. A history of repeated recurrences of colitis after respiratory infections may, however, in the occasional case, warrant removal of the tonsils, even in the absence of a history of acute tonsillitis.

It is generally considered sound practice to remove definitely infected tonsils and pulpless or periapically infected teeth, because a specific causative organsim may be dormant, waiting for favorable circumstances or a change in its own life cycle to cause an exacerbation, or because a nonspecific focus of infection tends to undermine the normal defenses of the body.

In the summer, traumatization of the bowel in its broadest sense presents an important hazard which should lend itself to satisfactory control. Epidemic diarrhea, food poisoning, seasonably abundant and cheap, coarse-fibered vegetables and an inordinate excess in the intake of fluids serve individually or in combinations to render the colon susceptible to reactivation of the disease. At all times strenuous catharsis (especially before operation) and superfluous irrigations or irrigations with caustic solutions are to be avoided. If it is realized that the end-results of healing may cause clinical pseudo-activity after all of the pathologic activity has subsided, overtreatment of the colon by well-intentioned physicians will be reduced materially. Surgical manipulation of a rectum or colon already injured by the ravages of chronic ulcerative colitis is undertaken with a forbidding risk and should be confined to imperative measures such as simple drainage of an abscess. To accord conservative expectant treatment and cautious surgical operation at the optimal time are trustworthy principles.

The grouping of emotional and physical strains as predisposing factors of recurrences in the third and fourth decades of life is evidently a reflection of the economic and social stresses which are most active during that time. The psychoanalytic studies made by Murray [3] in cases of chronic ulcerative colitis and the observations of numerous other investigators afford convincing evidence of the causal relationship of emotion to hypermotility, hypersecretion and spasticity of the colon. So far as possible, all stimuli which will upset the patient's nervous system are to be avoided. The patients soon gain a remarkable insight into their disease, so that minor setbacks have an unduly depressing effect on them. The physician must concern himself particularly with maintaining the patient's morale and helping him regain an optimistic view of the situation.

In using the diplostreptococcus vaccine during periods of quiescence, precautions against contamination or freezing are essential. By means of a carefully taken history and proper skin tests, hypersensitivity should be excluded, and the initial dose should not exceed 0.1 cc. of the vaccine, given subcutaneously. Increases must be gradual; systemic reactions are best avoided. At any signs of increased intestinal activity, a short period of rest followed by a reduced dose will be found advantageous.

Quiescent and adequately treated ulcerative colitis may be no contraindication to pregnancy or to necessary abdominal surgical operation.

Prominent among the prodromal symptoms when exacerbations are imminent are malaise, general exhaustion and fatigue, paresthesia of the abdominal wall, migratory pains in the flanks, aching joints and the appearance of superficial sores on the tongue and buccal mucous membrane. At such times, as well as during the premenstrual period, the prophylactic measures outlined deserve particular attention.

SUMMARY

Recurrences in a series of 209 medical and 23 surgical cases of chronic ulcerative colitis have been studied for predisposing and precipitating factors. Acute infections of the upper part of the respiratory tract initiated attacks in 57 per cent of the cases in which predisposing factors were recorded. Overexertion and emotional upsets were factors in 13 per cent; various conditions which traumatized or increased the irritability of the gastro-intestinal tract were factors in 12 per cent, and the removal of oral foci of infection was a factor in 5 per cent. The incidence of recurrences was lowest during the summer and reached its

3. Murray, C. D.: Psychogenic Factors in the Etiology of Ulcerative Colitis and Bloody Diarrhea, Am. J. M. Sc. **180**:239 (Aug.) 1930.

peak during the winter. A general relationship between the season and the etiologic agent is shown. Frequency of recurrences decreased with each decade of life. The situation and the extent of the lesion did not influence the frequency of recurrences. In cases in which a short-circuiting operation on the bowel had been made recurrences were common, and the relative importance of the precipitating agents was similar to that in cases in which treatment was medical. The distinction between clinical and pathologic activity is made. The prophylactic care of chronic ulcerative colitis in the quiescent stage is considered.

CORONARY THROMBOSIS

PERFORATION OF THE INFARCTED INTERVENTRICULAR SEPTUM

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Acquired perforation of the infarcted interventricular septum is a rare condition which is infrequently diagnosed. The only reported case in which an antemortem diagnosis was established is that of Brunn in 1923. The purpose of this report is to present another case of this complication of coronary thrombosis and to review the subject completely. I shall also attempt to present the criteria which make this condition, rare as it is, one that is clinically easily recognizable.

Krumbhaar and Crowell,[1] in 1925, gathered from the literature 654 cases of nontraumatic rupture of the heart, almost all secondary to coronary occlusion. At present the total is well over 700. From these figures it is evident that rupture of the heart is not rare. However, there are recorded only 17 cases of perforation of the infarcted interventricular septum, or nearly 3 per cent of all reported nontraumatic ruptures of the heart. With the addition of this case the total is brought to 18. The accompanying table lists all the cases recorded up to 1933. It will be seen that there were 13 men and 5 women affected; the ages were between 46 and 81 years, the average being 61.

Excluded from this series are all traumatic cases and ruptures caused by abscesses and parasitic cysts. All perforations at the base of the septum, which include congenital defects of the septum, rupture of congenital aneurysms of the undefended space and of the right aortic sinus of Valsalva, and ulcerative defects caused by bacterial endocarditis, are also excluded. This report deals only with the cases of coronary thrombosis which result in infarction of the septum and perforation.

REPORT OF A CASE

History.—I. A., a housewife, aged 60, admitted to the hospital on Dec. 21, 1932, for four years had arterial hypertension with a systolic pressure as high as 240 mm. of mercury. The family physician stated that during this period no

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From the Medical Service of Dr. B. S. Oppenheimer and the Laboratories of the Mount Sinai Hospital.

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* Eugene Meyer, Jr., Fellow in Pathology.

1. Krumbhaar, E. B., and Crowell, C.: Spontaneous Rupture of the Heart, Am. J. M. Sc. **170**:828 (Dec.) 1925.

Case Author	Age	Sex	Murmurs and Thrills	Location of Thrombosis	History Characteristic of Coronary Occlusion	Location of Rupture in the Septum	Size of the Rupture	Duration of Life in Days After Perforation	Comment on the Coronary Arteries
1. Latham [2].....(1)	61	M	Systolic thrill and rough murmur	Not noted	+	Posterior	Pin point	1	Atheromatous deposits
2. Latham [2].....(2)	60	M	Not noted	Not noted	+	Not indicated	Less than 2 in.	..	Arteriosclerosis with bony transformation
3. Beith [4].....	79	M	Not noted	Not noted	+	Middle	About 1½ in.	..	Arteriosclerosis with bony transformation
4. Peacock [5].....	62	M	Not noted	Not noted	±*	Lower half	Large	..	Arteriosclerosis with bony transformation
5. Pergami [6].....	60	M	Not noted	Not noted	+	Not indicated	.....	..	Not described
6. Grosse [7].....	52	M	Not noted	Left anterior descending artery	+	Middle, anteriorly	2 cm.	..	
7. Youmans [8].....	52	F	Systolic thrill and blowing murmur	Not noted	+	Lower half	6 by 3 mm.	..	Left anterior descending artery occluded by a fibrous plaque
8. Brunn [9].....(1)	46	M	Systolic thrill and murmur; soft diastolic murmur	Left anterior descending artery	+	Lower half	3 by 1 cm.	..	
9. Brunn [9].....(2)	52	M	Systolic thrill and murmur; short diastolic murmur	Right coronary and posterior descending arteries	+	Lower half	4 by 2 cm.	..	Sclerotic narrowing of left anterior descending artery
10. Martin and Waugh [10].....	52	M	Systolic loud murmur	Not noted	+	Lower half	Jagged (1 by 3 cm.)	10	"Obliterating endarteritis" of left anterior descending artery
11. Hyman [11].....	52	M	Shrill systolic murmur	Left anterior descending artery	+	Lower half	Large	>1	Sclerosis of both coronary arteries
12. Freeman and Griffin [12] (1)	60	M	Systolic thrill and loud murmur	Examination incomplete	±*	Lower half	Finger tip	1	Marked sclerosis of both coronary arteries
13. Freeman and Griffin [12] (2)	70	F	Systolic thrill and loud murmur	Examination incomplete	+	Lower half	Match stick	2	Sclerosis of both coronary arteries
14. Rintelen [13].....	73	F	Systolic thrill and murmur	Left anterior descending artery	+	Lower half	Wide catheter	..	Sclerosis of both coronary arteries
15. Bucciantí and Supino [14]....	70	F	Rough systolic thrill	Left anterior descending artery	+	Lower half	> 1 cm.	..	
16. Benson et al.[15].....(1)	60	M	Not noted	Left anterior descending artery	±*	Posterior	2 cm.	..	
17. Benson et al.[15].....(2)	81	M	Loud systolic murmur	Right coronary artery	+	Lower half	1 cm.	..	Left coronary artery closed by an old thrombus
18. Sager.....	60	F	Systolic thrill and loud murmur	Left anterior descending artery	+	Lower half	Pin point	..	Narrowing of right coronary artery by sclerosis

cardiac murmurs were audible. Her last illness began five days before hospitalization, with constricting pain across the chest and syncope. There was constant substernal and epigastric boring pain radiating upward into the neck. She perspired profusely, while her body felt "hot and cold all over." She was dyspneic and orthopneic. The output of urine was diminished.

Physical Examination.—The patient was well developed, dyspneic and orthopneic, with grayish cyanosis of the skin, and was bathed in a cold sweat. The cervical veins were distended. Examination of the lungs gave negative results. The heart was enlarged to the left in the fifth intercostal space. There was a rough systolic precordial thrill and a loud harsh systolic murmur, both of which were maximal at about 4 cm. to the left of the sternum in the fourth and fifth intercostal spaces and were transmitted to the left axilla and to the back just beneath the left scapula. The second aortic sound was louder than the second pulmonic. The blood pressure was 165 systolic and 95 diastolic. The pulse was rapid and regular. The liver was palpable 3 cm. beneath the right costal margin; there was no edema of the ankles. The temperature was 100.4 F.

Laboratory Examination.—Examination of the blood revealed: hemoglobin (Sahli), 76 per cent; white blood cells, 14,000 per cubic millimeter, and polymorphonuclear leukocytes, 82 per cent. The venous pressure by the direct method was 18 cm. of water; the blood urea nitrogen, 36 mg., and the blood sugar during fasting, 360 mg. per hundred cubic centimeters. Examination of the urine showed a specific gravity of 1.032; sugar, 3.3 mg. per hundred cubic centimeters; no acetone; a slight trace of albumin. Microscopic examination revealed a few hyaline casts; the output was about 450 cc. daily. An electrocardiogram showed low voltage in all leads; the main deflection of the Q R S complex inverted in lead I; the R T transition in all leads was off the baseline; the Q wave in lead III was not accentuated.

Clinical Diagnosis.—The condition was diagnosed as: essential hypertension; coronary sclerosis; acute coronary thrombosis; infarction and rupture of the interventricular septum, and diabetes mellitus.

Course.—The symptoms did not abate. On the day preceding the patient's death râles were heard throughout the entire field of the lungs. The blood pressure had dropped to 96 systolic and 72 diastolic. The skin was cold and clammy; the lips, cyanotic. The temperature had risen to 101.4 F. Death occurred in pulmonary edema five days after admission to the hospital.

Postmortem Examination (by Dr. Sager and Dr. Hitzig).—The anatomic diagnosis was : acute thrombosis of the anterior descending branch of the left coronary artery; marked arteriosclerotic narrowing of the posterior descending branch of the right coronary artery; acute myomalacia of the apex of the left ventricle, both left papillary muscles and the lower half of the interventricular septum, with perforation of the latter; parietal thrombosis of the left and right ventricles; hypertrophy and dilatation of both ventricles; localized pericardial adhesion; pulmonary edema; pulmonary emphysema; universal pleural adhesion; pulmonary arteriosclerosis; advanced arteriolosclerosis of the kidneys, and chronic passive congestion of the viscera.

Macroscopic Examination of the Heart: The heart weighed 500 Gm. The pericardium was smooth except over an area of about 4 cm. in diameter on the anterior surface of the left ventricle near the apex, where the pericardium was adherent but easily separated. The heart had a globular shape, and the apex was formed entirely by the left ventricle. The apical third of the left ventricle border-

ing on the interventricular septum anteriorly was soft and could be easily indented with the finger while the rest of the ventricle was firm. The right ventricle was markedly dilated and slightly hypertrophied. Within the apex of the right ventricle was an almond-shaped, grayish-red thrombus, which adhered to the columnae carneae and to the apical portion of the septum. Several of the columnae carneae in this region were greenish gray.

Saline solution poured through the aorta into the unopened left ventricle passed into the right ventricle through an opening hidden deeply between the

Fig. 1.—View of the right ventricle, showing the interventricular septum with a ureteral catheter in the septal defect.

columnae carneae at a point about 3 cm. above the apex of the ventricle. This opening would otherwise have been overlooked. After the left ventricle was opened, this aperture could also be seen by holding the heart up to the light (fig. 1).

The left ventricle was markedly hypertrophied but only slightly dilated. The apex and the lower half of the septum were relatively thin. The lower half of the septum was grayish green and necrotic, and bulged slightly to the right. A conical depression about 7 mm. in diameter was situated 3 cm. above the apex of the left ventricle; a ureteral catheter inserted into it passed upward, anteriorly and to the right, through the interventricular septum to reappear in the right ventricle at the point through which the saline solution had escaped (fig. 2). The lower

third of the left ventricle anteriorly and both papillary muscles were grayish green with hemorrhagic streaks. There were gray thrombi adherent to the endocardium in the region of the apex. The auricles and valves showed no pathologic changes.

The coronary ostia were patent. Both arteries showed extensive arteriosclerosis. The anterior descending branch of the left coronary artery was markedly narrowed by arteriosclerosis, and at a point 2.5 cm. distal to its origin was closed by a red thrombus which extended for a distance of 3 cm. The posterior descending branch of the right coronary artery was thickened by subintimal fatty deposits and was markedly narrowed. The aorta presented a marked degree of arteriosclerosis with calcification and ulceration of its thoracic and abdominal portions.

Microscopic Examination.—The myocardium of the anterior wall of the left ventricle where it joins the septum was necrotic. Nuclei were absent, and the

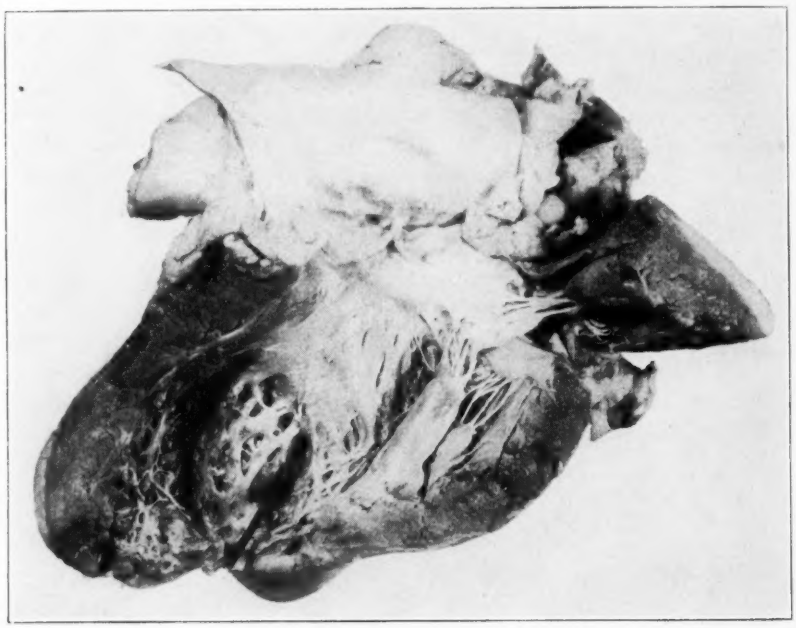

Fig. 2.—View of the left ventricle, showing the interventricular septum with a conical depression where the catheter enters the defect.

muscular striations not discernible; the "ghost" myocardium stained lightly and diffusely with eosin. There were bandlike infiltrations along the septums, consisting chiefly of polymorphonuclear leukocytes and macrophages. Toward the periphery of the section were numerous macrophages loaded with iron-containing pigment, and there were young fibroblasts invading the necrotic area.

The anterior descending branch of the left coronary artery revealed a thick intima composed of fibrous tissue with heavy deposits of fat and calcium. Much of the fat was doubly refracting. There was extensive new formation of elastica in the intima. The lumen was closed by a clot consisting of interlacing strands of fibrin with many enmeshed erythrocytes. Organization by fibroblasts had begun. The media was thinned out through much of its circumference. In the adventitia were small collections of lymphocytes. The posterior descending branch of the right coronary artery showed a similar process, but without thrombosis.

CASES IN THE LITERATURE

Latham [2] in his lectures on the heart, published in 1845, first reported rupture of the infarcted septum. In his first case he presented a description of the clinical phenomena, to which nothing can be added today. Unfortunately, in his case, as in many of the cases of disease of the coronary arteries described in the early literature, the examination of the coronary arteries for thrombosis was not done completely or was not completely recorded. However, it will be apparent from the typical history of occlusion of the coronary arteries and from the details of the postmortem examination that a thrombosis probably did exist. Libman [3] has pointed out, however, that in certain cases myocardial infarction may occur without an acute coronary thrombosis. The patient was a man, aged 61, a corpulent gouty cripple. He suddenly experienced a severe constant pain which "occupied the entire front chest and passed along both clavicles to the top of the shoulders." On the third day of his illness he was given vinum colchici, on the fourth, the pain disappeared, but on the sixth it reappeared with aggravated severity. For the first time a systolic precordial murmur not transmitted to the arteries was heard. "He was deadly pale, and from the center to the extremities of the body he was cold as marble, and streaming with perspiration, but his pulse was of good strength. . . . I staid with him through the night, still giving at intervals opium and aether and ammonia, but all to no purpose." He died the next day. At necropsy although the rest of the myocardium seemed normal, "the septum was pale and soft, manifestly in consequence of fatty degeneration. In the septum at its posterior junction with the parietes there was an oblique rent passing through it from ventricle to ventricle. On the side of the left ventricle it was an inch and a half in length, on the side of the right it just opened at a point, so that the aperture was not at first noted from the right ventricle. The coronary arteries contained some atheromatous deposits, but were quite pervious."

Latham's second case was observed clinically by another physician; only the postmortem specimen was available to him. It was the heart of a man, aged 60, who had suffered from angina pectoris. Three days previous to his death he experienced an extraordinarily severe attack of substernal pain which was constant. A rupture of the septum was found. The coronary arteries were thickened and "contained bony matter deposited between the coats." Mr. Paget and Dr. Ormerod described the muscular tissue near the perforation as being "evidently disorganized, for it appeared as irregular granular cords without any transverse striae, which were elsewhere well marked."

The second report was that of Beith [4] in 1850. A man, aged 79, fell, and for five days thereafter felt a constricting pain in the chest radiating to the back of the left shoulder. Death ensued. The heart weighed 17 ounces (481.9 Gm.). There was a dense ossifying obstruction of the anterior descending branch of the left coronary artery. Midway between the apex and the base of the interventricular septum was a rupture about 1½ inches in diameter, its edges covered with fibrin. Auscultatory details were not mentioned.

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2. Latham, P. M.: Lectures on Subjects Connected with Clinical Medicine Comprising Diseases of the Heart, London, Longmans, Brown, Green and Longmans, 1845, vol. 2, p. 168.

3. Libman, E.: The Importance of Blood Examination in the Recognition of Thrombosis of the Coronary Arteries and Its Sequelae, Am. Heart J. **1**:121 (Oct.) 1925.

4. Beith: A Case of Septal Rupture, Tr. Path. Soc. London **3**:69, 1850.

Peacock,[5] in 1854, demonstrated the heart of a man, aged 62, who had slight pain in the chest for four or five days. On the night of his death he began to breathe rapidly and hurried to bed. He denied that he was uncomfortable. No physical findings are mentioned. The heart weighed 14 ounces (396.9 Gm.). One third of the way from the apex to the base there was a large rupture of the interventricular septum. The myocardium about the rupture was flaccid. The coronary arteries were studded with atheroma and bone. The aortic valve was less capacious than normal.

Pergami,[6] in 1876, reported the case of a man, aged 60, who died suddenly with terrifying angor animi and pain in the left side of the chest. A circular opening was found in the interventricular septum. It was larger on the left side of the septum than on the right. The myocardium about the defect was degenerated. The coronary arteries were not described.

The next case was described in 1906. Grosse[7] studied the heart of a man, aged 52, who had been well until a year previous to his death, when he began to complain of precordial pain and dyspnea on exertion. After a long rest he felt sufficiently well to return to his work. His pain suddenly reappeared with great severity, and he became orthopneic. He was later taken to the hospital, but died before a satisfactory physical examination could be made. In the middle of the interventricular septum near the anterior ventricular wall was an oval defect 2 cm. in length with a thrombus attached to the edges. The anterior descending branch of the left coronary artery was narrowed throughout; 3 cm. below its origin it was obstructed by a thrombus 18 mm. in length.

In 1921 Youmans[8] reviewed the literature on perforation at the base of the septum, but his own case belongs to the group here discussed. A woman, aged 52, had severe prolonged attacks of angina pectoris with dyspnea, orthopnea and edema of the feet for ten days before hospitalization. The heart sounds were regular and rapid. A precordial thrill was palpable, and there was a blowing precordial murmur difficult to time and loudest at the left of the sternum in the fourth and fifth intercostal spaces. At necropsy, an aneurysmal pouch in the left ventricle "antero-laterally to the right and opposite to the interventricular septum in its lower half" was found. A few centimeters above the apex was a defect in the interventricular septum, 6 by 3 mm., the edges being covered by an adherent thrombus. The surrounding myocardium was softened. The anterior descending branch of the left coronary artery was occluded by a fibrous plaque.

Brunn,[9] in 1923, described 2 important cases in detail. The first case was that of a man, aged 46, who five days before hospitalization began to experience severe constant substernal pain with angor animi. His skin was gray and livid, and there was edema of the legs. The systolic blood pressure was 136. The heart borders were widened. Over the lower portion of the sternum and to the left in the fourth

5. Peacock: A Case of Rupture of the Septum, Tr. Path. Soc. London **5**:102, 1854.

6. Pergami, E.: Ulcera perforante del setto del cuore: morte subitanea, Ann. univ. di med. e chir. **237**:42, 1876.

7. Grosse, B. J.: Ein Fall von Ruptur der Herzkammerscheidewand mit retrograder Emboli in der Leber, Inaug. Dissert., Rostock, C. Bolat, 1906; quoted by Rintelen.[13]

8. Youmans, J. B.: Perforation of the Interventricular Septum of the Heart, with Report of a Case, Arch. Int. Med. **28**:495 (Oct.) 1921.

9. Brunn, F.: Zur Diagnostik der erworbenen Ruptur der Kammerscheidewand des Herzens, Wien. Arch. f. inn. Med. **6**:533 (Oct.) 1923.

and fifth intercostal spaces a rough systolic thrill was palpable. A long systolic murmur was audible over the middle of the sternum; two days later a soft diastolic murmur developed in the same area. The liver was tender and palpable three fingerbreadths beneath the right costal margin. The patient died on the day following entrance to the hospital. The clinical diagnosis had been endocarditis with rupture of a papillary muscle. An aneurysmal pouching was found at the apex of the left ventricle. About 3 cm. above the apex there was a tear in the septum, 3 by 1 cm., surrounded by a considerable area of myomalacia. There was a fresh thrombus in the anterior descending branch of the left coronary artery.

Brunn's second case was that of a man, aged 52, who for a week had substernal pain radiating to the left arm and with it a sense of impending dissolution. His hands were cold and cyanotic. He was dyspneic and coughed up red sputum. The radial pulse on the right was small; on the left it was absent. Cardiac dulness was increased. A fine systolic thrill was felt and a rough systolic murmur heard over the lower part of the sternum. The liver was palpable below the costal margin. Four days later a short diastolic murmur appeared, all pulses disappeared, and shortly afterward the patient died. In view of Brunn's experience with the preceding case, he made a diagnosis of septal perforation with embolism of the subclavian and iliac arteries. At necropsy, myomalacia of the interventricular septum and the posterior wall of the left ventricle was found. There was a perforation of the septum, 4 by 2 cm., situated about 3 cm. above the apex. The left ventricle was hypertrophied. There was marked arteriosclerotic narrowing of the anterior descending branch of the left coronary artery and a thrombosis of the right coronary artery extending into its posterior descending branch. This is the only recorded case in which the antemortem diagnosis of perforation of the infarcted septum was proved.

In 1925 Martin and Waugh[10] reported the case of a man, aged 52, who was suddenly seized with an attack of acute precordial pain. Examination of the heart shortly after the onset gave negative results, but on the following day a loud systolic precordial murmur was heard. He died in shock ten days after the onset. The left ventricle was hypertrophied. At the apex of the heart was a soft necrotic aneurysmal bulge. About 3 cm. above the apex in the softened septum was a star-shaped perforation. "Obliterating endarteritis" of the anterior descending branch of the coronary artery was reported.

Hyman,[11] in 1929, presented the case of a man, 52 years of age, in whom a sudden onset of severe abdominal pain suggested the diagnosis of ruptured peptic ulcer. The heart sounds were feeble. He was cold, clammy and pulseless. Four hours later a shrill systolic murmur was heard over the precordium. Spontaneous rupture of the heart was suggested, but the site of rupture was not localized. The electrocardiogram revealed abnormal R T transitions in leads I and II with inversion of the T waves in all leads; the Q wave in lead III was not deep. A perforation of the interventricular septum was found near the apex. Both coronary arteries were sclerotic; there was a thrombus occluding the anterior descending branch of the left coronary artery.

Freeman and Griffin,[12] in 1932, added 2 cases. Their first case was that of a man, aged 60, who was hospitalized because of dyspnea and cyanosis. No cardiac

10. Martin, C. F., and Waugh, T. R.: Rupture of the Septum Ventriculorum, Ann. Clin. Med. **4**:183 (Sept.) 1925.

11. Hyman, A. S.: Spontaneous Rupture of the Heart; Perforation of the Interventricular Septum, Ann. Int. Med. **3**:800 (Feb.) 1930.

12. Freeman, W., and Griffin, E. D.: Cardiac Rupture with Perforation of the Interventricular Septum, Am. Heart J. **7**:732 (Aug.) 1932.

murmurs were heard. His blood pressure was 102 systolic and 68 diastolic. The patient later went into shock, becoming pale, cold and clammy. A systolic thrill was felt, and a loud systolic murmur was audible over the entire precordium. The pulse was absent at both wrists; the liver was palpable two fingerbreadths beneath the costal margin. The electrocardiogram showed abnormal R T transitions in all leads, and inverted T waves in lead I. The Q waves in lead III were not deep. Leukocytosis was present. A diagnosis of "acute aortic stenosis," ruptured aortic leaflet or dissecting aneurysm was made. At necropsy the left ventricle was seen to be hypertrophied. There was a perforation about 1 cm. in diameter in the interventricular septum near the apex. There was severe arteriosclerosis of both coronary arteries with almost complete obliteration of the anterior descending branch of the left coronary artery. (The coronary arteries were not completely dissected in order to preserve the specimen for museum purposes.)

Their second case was that of a woman, aged 70, who was suddenly seized with severe abdominal pain radiating to the left arm and scapula. On admission, except for a state of shock and slight edema of the ankles, the cardiac status was negative. The electrocardiogram suggested coronary thrombosis. On the fourth day a loud systolic murmur and a marked thrill appeared. The blood pressure was 150 systolic and 60 diastolic. She died on the fifth day. The diagnosis made was acute coronary thrombosis. The interventricular septum was pale and soft with hemorrhagic areas; there was a perforation admitting a match 2 cm. above the apex. The coronary arteries were sclerotic, but the "location of the thrombus was not further investigated."

In 1932 Rintelen[13] reported the case of a woman, 73 years of age, who had complained of slight cardiac pain for many years. She suddenly felt weak, vomited and became dyspneic and cyanotic. Her heart was enlarged to the left and right. Over the entire precordium a thrill was felt and a murmur heard which was transmitted to the aortic area, where the second sound was absent. The second pulmonic sound was audible. She died within a few hours after hospitalization. The diagnosis was aortic stenosis. Postmortem examination revealed the left ventricle to be hypertrophied. There was a septal defect admitting a wide metal catheter 3 cm. above the apex of the left ventricle. The tissue about the rupture was hemorrhagic and fatty. Microscopic section showed necrosis of the myocardium. The anterior descending branch of the left coronary artery, 3.5 cm. from its origin, was narrowed and ulcerated by an arteriosclerotic process, and the lumen at this point was closed by a grayish-red thrombus.

Buccianti and Supino[14] also reported their case in 1932. A woman, aged 70, complained of pain in the upper part of the abdomen for several months. Shortly before her hospitalization the pain became excruciating. Cardiac decompensation was evident; the lips were cyanotic, the skin pale and the ankles edematous; the patient was dyspneic. The blood pressure was 155 systolic and 90 diastolic. The liver was palpable three fingerbreadths below the right costal margin. The heart was enlarged. There was a rough systolic precordial thrill and a rough systolic murmur within the apex replacing the first sound and obliterating the second. The R T transition was abnormal in lead II; the T wave was negative; the Q R S complex was low in lead I; there were nodal rhythm and atrioventricular dissociation. The Q wave in lead III was not deep. On the basis of the electrocardio-

13. Rintelen, F.: Zur Kenntnis des myomalazischen Septumdefektes und zur Spontanruptur des Herzens, Ztschr. f. Kreislaufforsch. **24**:375 (June 15) 1932.

14. Buccianti, E., and Supino, L.: Considerazione cliniche e anatomo-patologiche sull'infarto del miocardio, Clin. med. ital. **63**:1085, 1932.

gram, a diagnosis of coronary thrombosis with infarction of the interventricular septum was made. At necropsy an apical fibrous aneurysm of the left ventricle was found. About 4 cm. above the apex was a perforation in the septum less than 1 cm. in diameter. The anterior descending branch of the left coronary artery was calcified and thrombosed. No lesion was found in the junctional tissues to account for the atrioventricular block.

Benson, Hunter and Manlove,[15] in 1933, noted 2 cases of interventricular defect among 40 cases of rupture of the heart. The first case (case 33) was that of a man, aged 60, who was found dead in bed. There was a hemorrhagic adhesion of the pericardium to the posterior interventricular sulcus. The posterior paraseptal regions of the right and left ventricles and the septum itself were the seat of a hemorrhagic infarction with a ragged rupture 2 cm. in length in the posterior portion of the septum. The coronary orifices were patent. The branches of the left coronary artery were narrowed, and the left circumflex was blocked by an old white recanalized thrombus. The right coronary artery was closed by a fresh thrombus 2.5 cm. in length. The authors made a pathologic diagnosis of "septic infarct," "fresh thrombosis of the right coronary artery" and "probably syphilitic arteritis." By "septic infarct" they probably referred to the streaklike polymorphonuclear infiltrations commonly seen in myocardial infarcts, for they did not mention the finding of bacteria. Since the aorta was free from syphilis and the coronary orifices were patent, it is hardly likely that syphilis played any part in this case.

In the second case (case 34), a man, aged 81, had complained of pain in the upper part of the abdomen and in the right side of the chest for three years. Ten days before his death he became pale and dyspneic. Eight days later, on hospitalization, his heart was found to be enlarged 13 cm. to the left of the sternum. A loud systolic murmur was heard best over the mitral area and was transmitted to the axilla and to the back. The liver was three fingerbreadths beneath the costal margin. The blood pressure was 140 systolic and 70 diastolic. Four hours before death he went into a state of shock. The presence or absence of thrills was not mentioned. At necropsy a hemorrhagic pericarditis was found. The apex of the left ventricle was thin-walled. In the distal half of the muscular septum was a ragged rent 1 cm. in length. The anterior descending branch of the left coronary artery was occluded by a fairly recent reddish thrombus with recanalization. Microscopic examination at the edges of the rupture showed that "it had existed long enough to give rise to granulation tissue."

Faulkner, Marble and White[16] made statistical mention of a case of coronary thrombosis with rupture of the interventricular septum, but gave no details. Their case, therefore, has not been listed in the table.

COMMENT ON THE CLINICOPATHOLOGIC SYNDROME

In reviewing the cases presenting more complete clinical data, one notes that while the patients' symptoms are typical of acute coronary thrombosis, the cardiac signs are identical with those of congenital patency of the interventricular septum. In the face of such a coincidence,

15. Benson, R. L.; Hunter, W. C., and Manlove, C. H.: Spontaneous Rupture of the Heart, Am. J. Path. **9**:295 (May) 1933.

16. Faulkner, J. M.; Marble, H. C., and White, P. D.: The Differential Diagnosis of Coronary Occlusion and of Cholelithiasis, J. A. M. A. **83**:2080 (Dec. 27) 1924.

therefore, one is justified in assuming that a rupture of the infarcted septum has taken place. Application of this principle in the case here reported made it possible to predict the results of the postmortem examination. Of the cases in the literature, adequate clinical description is presented only in the following: Latham, (first case), Brunn, (both cases), Martin and Waugh, Hyman, Freeman and Griffin, (both cases), Rintelen, Buccianti and Supino, and Benson, Hunter and Manlove (second case). In all these cases the physical findings simulate closely those associated with Roger's disease. In rupture of the infarcted septum the defect is relatively small. On the principle that the smaller the aperture the louder is the murmur and the rougher the thrill, we must, therefore, expect the cardiac signs to be well marked even when the patient is moribund. On the other hand, in congenital patency, in which the septal opening is not infrequently very large, the typical murmurs may be absent.

Congenital defects are consistent with longevity while acquired defects are not, because in the latter the patients die of the myocardial infarction and not of the perforation. The small opening in the septum, although it gives rise to intense murmurs, does not seriously affect cardiac dynamics. One never sees the deep cyanosis of the later stages of congenital patency in acquired septal perforation, because the relative differences in pressure in the ventricular chambers are maintained even though the individual pressures are changed; furthermore, the clinical picture is usually attended by signs of shock; and the small defect, in any case, would hardly allow sufficient blood to pass from the right to the left ventricle to produce deep cyanosis.

One who has occasion to observe a case from the onset of the coronary occlusion before perforation has ensued, is impressed by the sudden appearance of the forceful thrill and murmurs which later signalize the perforation. Such was the experience of Latham (first case), Martin and Waugh, Hyman and Freeman and Griffin (both cases). In the case here reported the family physician gave assurance that the murmur and thrill were never heard before. However, one does not need this foreknowledge to make the diagnosis of perforation of the infarcted septum; the physical signs in conjunction with the clinical history are quite sufficient.

The symptoms and the general physical appearance of the patient are the same as those in myocardial infarction without perforation. There are moderate fever and leukocytosis. One observes the familiar signs of shock: grayish cyanosis, cold clammy skin and a small pulse. To these signs may be added various degrees of left cardiac failure, as shown by orthopnea, paroxysmal dyspnea and pulmonary edema, and sometimes of right cardiac failure, manifest by a deeper grade of cyanosis, an enlarged liver, peripheral edema, distended veins and an

elevated venous pressure. The blood pressure is low, or, if formerly high, becomes lower. The physical signs may include a pericardial friction rub, feeble quality of cardiac sounds and an enlargement which is usually referable to the effects of previous hypertension rather than to recent dilatation of the heart. In addition to these one finds the physical signs of Roger's disease. In typical cases a harsh systolic murmur and a rough systolic thrill are established over the precordium with their maximum intensity to the left of the sternum in the fourth and fifth intercostal spaces. The murmur is usually transmitted to the left axilla and subscapular region, but not to the great vessels. In the present case, the murmur was maximal farther to the left than usual, perhaps because of the marked hypertrophy of the left ventricle with a more transverse position of the heart. When the diameter of the defect in the septum enlarges to 2 cm, or more, a diastolic murmur may also be heard.

The electrocardiogram is typical of acute coronary artery occlusion. However, none of the cases of septal perforation in which the electrocardiogram is recorded shows the deep Q wave in lead III which has been regarded by some as characteristic of infarction of the septum.

At necropsy, the lower part of the interventricular septum is found infarcted to a greater or lesser degree, as is the adjacent anterior or posterior wall of the left ventricle and a small area of the right ventricular wall. In almost all cases on complete examination the cause of the infarction is found to be a thrombotic occlusion of the coronary arteries. Usually the anterior descending branch of the left coronary artery is thrombosed, while the posterior descending branch of the right is severely narrowed by arteriosclerosis. In the second case of Brunn and the first of Benson and his co-workers, the reverse situation existed —the posterior descendens (or the right coronary artery, as in the latter case) was thrombotic, and the anterior descendens was narrowed by arteriosclerosis. The infrequency of rupture of the septum when compared to rupture of the anterior and posterior walls of the left ventricle is explained by the rich anastomotic arterial supply of the septum, well demonstrated by Gross,[17] in studies of the coronary arteries by means of injection. One notes, therefore, with interest, the significance of the fact that in almost all the cases here reviewed, in which detailed pathologic studies were given, both the anterior and the posterior descending arteries were embarrassed.

The size of the perforation varies from defects admitting only a fine probe to those of about 3 cm. in the longest diameter. The narrower defects are frequently tortuous and difficult to find unless

17. Gross, L.: The Blood Supply of the Heart in Its Anatomical and Clinical Aspects, New York, Paul B. Hoeber, Inc., 1921, p. 85.

water or physiologic solution of sodium chloride is poured into the unopened left ventricle. For this reason cases must undoubtedly have been overlooked, the perforation not having been suspected clinically, and therefore not carefully searched for at necropsy.

Thus far all cases reported have been fatal; when calculable, death was found to ensue within ten days after the occurrence of the perforation. But as patients with cardiac infarction without perforation frequently recover, it is to be expected that occasionally in one of those with perforation the infarct may be repaired with scar tissue and the patient may survive. Under such conditions the perforation and, therefore, the physical signs would be expected to persist (unless the former were sealed by a thrombus or by scar tissue).

Cardiac infarction with rupture of a papillary muscle of the left ventricle is the only condition which may lead to confusion in the differential diagnosis. However, in rupture of the papillary muscle the heart is usually markedly widened; the systolic thrills and murmurs are even more bizarre and more pronounced, and a diastolic murmur is more common. The physical signs are either maximal at the apex or equally marked over the entire precordium. Voigt's [18] recent report on rupture of the papillary muscle presents a complete review of this subject.

Congenital patency of the interventricular septum, ruptured congenital aneurysm of the pars membranacea septi, and perforations complicating bacterial endocarditis are easily differentiated by the absence of the syndrome of coronary occlusion and by the comparative youth of most of the patients. In congenital patency, cyanosis, polycythemia, clubbed fingers and the differential facts mentioned at the beginning of this discussion are of additional aid. In bacterial endocarditis the familiar embolic phenomena as well as the result of blood culture will usually confirm the diagnosis.

SUMMARY

1. The literature on perforation of the infarcted septum in coronary thrombosis is reviewed, and an additional case with pathologic findings is reported.

2. The criteria for the diagnosis and differential diagnosis are discussed.

1 East One Hundredth Street.

18. Voigt, W.: Spontanruptur eines Papillarmuskels, zugleich ein Beitrag zur Gestalt des linken hinteren Papillarmuskels, Ztschr. f. Kreislaufforsch. **24**:667 (Nov. 1) 1932.

INSULIN AND SUGAR TOLERANCE IN THIN PEOPLE

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Comparatively little is known of the effect of insulin on sugar tolerance in nondiabetic persons. However, certain observations have been reported to suggest that the drug has an appreciable effect on this phase of metabolism. A temporary loss of carbohydrate tolerance during a period of administration of insulin was observed by Wilder, Smith and Sandiford [1] in the case of two obese patients and by Paul, Clark and Gibson [2] in five normal persons. Schellong and Kramer [3] made tests for the sugar tolerance of fourteen thin women before and during insulin therapy and noted a more rapid rise and an earlier fall in the curves for blood sugar during the period of treatment with insulin than during the control period. Fricke [4] administered dextrose by stomach tube to dogs without inducing glycosuria, but when the same dose of dextrose was combined with injections of insulin, glycosuria of short duration occurred in two and three hours.

Since insulin is now being used widely in the treatment of undernutrition in nondiabetic persons, it appeared of interest to study more particularly the effect of insulin on the sugar tolerance of such persons. This article, therefore, reports the results of tests for sugar tolerance which were carried out on twenty-five normal thin patients.

PLAN OF INVESTIGATION

The work reported here was carried on according to the following methods: The dextrose tolerance was observed before, during and after the administration of insulin in nine cases, during and after a course of insulin therapy in seven cases and only after insulin had been omitted in nine cases. In the cases studied during a period of treatment

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1. Wilder, R. M.; Smith, F. H., and Sandiford, I.: Observations on Obesity, Ann. Int. Med. **6**:724, 1932.

2. Paul, W. D.; Clark, B. B., and Gibson, R. B.: Transient Hyperglycemia and Glycosuria Following Discontinuation of Insulin Given Nondiabetic Patients, Proc. Soc. Exper. Biol. & Med. **30**:353, 1932.

3. Schellong, F., and Kramer, H.: Ueber die Ursachen der alimentären Hyperglykämie bei Kohlehydratkarenz (zugleich ein weiterer Beitrag zur Wirkungsweise der Insulin Mastkuren), Klin. Wchnschr. **7**:1726, 1928.

4. Fricke, G.: Glykosurie durch Insulin, Klin. Wchnschr. **5**:1927, 1926.

with insulin, 10 or 15 units of the drug were taken three times a day for from one to twelve weeks before the test was made, and in the cases studied after insulin was omitted, a period of from three days to two years after the discontinuance of insulin therapy elapsed before the final test was made. A standard dose of 100 Gm. of dextrose was employed. This was mixed with 250 cc. of water, flavored with 50 cc. of lemon juice, chilled and ingested after the patient had fasted for at least fourteen hours. The concentration of sugar in the blood and urine was determined in specimens taken during fasting and at intervals of one-half, one, two and three hours after the ingestion of the dextrose mixture, the determinations of blood sugar being made on 0.1 cc. samples of venous blood according to the micromethod of Folin and Malmros.[5] The test for sugar in the urine was made with Benedict's solution.

The group studied comprised ten men and fifteen women whose ages varied from 23 to 58 years. Their weights ranged from 85 to 140 pounds (38.55 to 64.5 Kg.) before treatment with insulin, from 91 to 153 pounds (41.27 to 69.4 Kg.) during insulin therapy and from 85 to 180 pounds (38.55 to 81.54 Kg.) after the discontinuance of insulin therapy. Each was more than 15 pounds under standard weight for age, sex and height before the first injection of insulin. None had any demonstrable physical abnormality.

CURVES FOR BLOOD SUGAR

The results obtained can be divided into three groups. In one group, consisting of six persons, the curves for blood sugar were entirely normal throughout the experiment, and the specimens of urine remained persistently sugar-free.

In a second group of six cases, the curves for blood sugar remained essentially normal during the different phases of the study, but during the period of administration of insulin, glycosuria developed. It is interesting to note that in spite of normal levels for blood sugar, there developed in the patients with insulin a concentration of from 0.1 to 1.7 per cent of sugar in the urine, yielding a total excretion of from 0.025 to 0.5 Gm. This appeared one or two hours after the ingestion of dextrose and was transitory.

In the third group, comprising four cases, a considerable increase in the blood sugar developed after the dextrose meal while insulin was being taken. The peak of hyperglycemia occurred one-half or one hour after the ingestion of the sugar and was accompanied by glycosuria in one or two hours. This reached a concentration of from 0.2 to

5. Folin, O., and Malmros, H.: An Improved Form of Folin's Micro Method for Blood Sugar Determinations, J. Biol. Chem. **83**:115, 1929.

TABLE 1.—*Sugar Tolerance Showing Normal Curves for Blood Sugar Without Glycosuria* *

Patient	Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose Before Administration of Insulin: Number of Hours After Ingestion of Dextrose					Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose During Period of Insulin Therapy: Number of Hours After Ingestion of Dextrose					Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose After Discontinuing Insulin Therapy: Number of Hours After Ingestion of Dextrose					Length of Time After Discontinuing Insulin Therapy
	Fasting	½	1	2	3	Fasting	½	1	2	3	Fasting	½	1	2	3	
1.	125	151	148	133	80	112	140	146	122	80	111	156	...	99	85	4 days
2.	92	98	105	102	72	117	140	103	95	94	94	128	97	82	74	1 week
3.	103	175	166	133	109	89	100	132	133	80	97	118	99	87	80	1 week
4.	...	...	...	...	...	88	119	125	88	85	76	121	104	98	68	4 days
5.	...	...	...	...	...	87	144	156	124	70	90	154	154	114	83	5 days
6.	...	...	...	...	...	133	144	151	144	104	99	148	148	138	101	1 week

* In tables 1 to 4, values are expressed in milligrams per hundred cubic centimeters.

TABLE 2.—*Sugar Tolerance Tests Showing Normal Curves for Blood Surgar with Glycosuria During Treatment with Insulin*

Patient	Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose Before Administration of Insulin: Number of Hours After Ingestion of Dextrose					Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose During Period of Insulin Therapy: Number of Hours After Ingestion of Dextrose					Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose After Discontinuing Insulin Therapy: Number of Hours After Ingestion of Dextrose					Length of Time After Discontinuing Insulin Therapy
	Fasting	½	1	2	3	Fasting	½	1	2	3	Fasting	½	1	2	3	
7.	96	119	144	88	77	100	146	154*	114*	96	89	149	160	97	85	5 days
8.	100	148	125	113	100	85	136	147*	97	95	83	160	102	74	72	3 days
9.	93	148	149	125	105	104	167	141*	92*	91	105	166	138	125	102	1 week
10.	75	100	111	85	73	108	137	125*	106	80	105	133	133	87	80	1 week
11.	100	100	125	95	84	103	130	141*	143	108	98	103	124	111	100	1 week
12.	...	...	...	...	...	98	132*	156	100	66	97	117	130	80	86	2 weeks

* From 0.025 to 0.5 Gm. of sugar was excreted in the urine.

TABLE 3.—*Tests for Sugar Tolerance Showing Hyperglycemia and Glycosuria with Insulin Therapy*

Patient	Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose Before Administration of Insulin: Number of Hours After Ingestion of Dextrose					Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose During Period of Insulin Therapy: Number of Hours After Ingestion of Dextrose					Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose After Discontinuing Insulin Therapy: Number of Hours After Ingestion of Dextrose					Length of Time After Discontinuing Insulin Therapy
	Fasting	½	1	2	3	Fasting	½	1	2	3	Fasting	½	1	2	3	
13.	79	116	85	80	74	114	154	185*	104*	102	109	109	109	116	102	2 weeks
14.	...	...	...	...	...	104	196	200*	103*	80	102	141	126	108	100	10 weeks
15.	...	...	...	...	...	100	170*	171*	111*	97	84	103	124	105	100	1 week
16.	...	...	...	...	...	107	158	196*	103*	100	125	180	200	149†	95	6 days
16.	...	...	...	...	...	...	...	...	...	...	105	145	150	128	100	3 months

* From 0.08 to 0.4 Gm. of sugar was excreted in the urine.
† The slightest possible trace of sugar was present in the urine.

1.8 per cent of sugar in the urine, yielding a total excretion of from 0.08 to 0.4 Gm. of sugar. The curve for blood sugar in these instances was of the type usually encountered in mild diabetes and suggested, definitely, a transitory depression of sugar tolerance.

In order to ascertain whether the sugar tolerance was in any way permanently impaired by insulin, tests for sugar tolerance were carried out on a group of nine patients who had received the drug over a long period of time. The final test for sugar tolerance was made from four months to two years after administration of the drug had stopped. For all of these patients the curves for blood sugar were normal, and there was no glycosuria.

Finally, since a decreased tolerance to 100 Gm. of dextrose occurred in some of the patients while they were taking insulin, it appeared of

TABLE 4.—*Sugar Tolerance After the Omission of Insulin* *

	Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose After Discontinuing Insulin Therapy					
		Number of Hours After Ingestion of Dextrose				Length of Time After Discontinuing Insulin
Patient	Fasting	½	1	2	3	Therapy
17	89	136	121	109	80	16 months
18	80	156	166	122	80	11 months
19	94	118	110	109	80	17 months
20	96	...	111	91	...	13 months
21	98	133	111	87	84	2 years
22	101	128	...	129	118	14 months
23	80	110	178	101	98	2 months
24	105	...	133	105	100	2 years
25	101	120	72	96	81	4 months

* No tests for sugar tolerance were made on these patients before or during treatment with insulin.

practical value to test the urine and the blood for sugar while the patients were taking their usual diets during various periods of observation. With this in mind, occasional samples of urine or of blood were collected after various meals and examined for sugar. In no instance was there any glycosuria or hyperglycemia either during or after the period of insulin therapy.

COMMENT

At present the cause of the results obtained in this study is largely a matter of speculation. The appearance of glycosuria without hyperglycemia suggests that insulin may have an effect on the kidney, causing a decreased renal threshold to sugar or an increased permeability to it. Such an effect, however, may appear improbable in the light of evidence obtained by other workers. Rabinowitch [6] showed that in certain diabetic persons the renal threshold rises substantially after the use of

6. Rabinowitch, I. M.: Observations on the Altered Renal Threshold for Sugar in Insulin—Treated Diabetics, Brit. J. Exper. Path. **7**:352, 1926.

insulin, and van Creveld and van Dam's [7] experiments on surviving frogs' kidneys indicate that insulin tends to decrease rather than to increase the permeability of the glomerular membrane to sugar.

The appearance of a transient glycosuria after the administration of insulin and sugar with an elevation of the level for blood sugar suggests that insulin may cause an increase in the rate of absorption of sugar from the gastro-intestinal tract or possibly a temporary but perceptible decrease in the pancreatic function.

That insulin increases absorption of food has already been proposed by Blotner [8] and by Koref and Mautner.[9] Cori and Cori,[10] too, have shown by experiments on rats that insulin increases the rate of absorption of dextrose from the intestinal tract.

There is evidence to suggest that insulin may cause a temporary decrease in pancreatic function. McJunkin and Roberts [11] found that injections of insulin inhibited the mitotic activity of the pancreatic islet cells in young rats. Wilder, Smith and Sandiford [1] and Paul, Clark and Gibson [2] explained the phenomenon of glycosuria and hyperglycemia following administration of insulin as due to a diminished irritability of the rested pancreas or to inhibition of the normal islet secretion in compensation for the excessive amount of insulin present following its injection.

Such a suppression of pancreatic function might be analogous to the reaction of certain endocrine glands, such as the ovaries and the parathyroid glands, when the endocrine products derived from those glands are administered. For example, Graber and Cowles [12] have inhibited normal ovarian activity with corpus luteum extracts and Goldman and Aub [13] have depressed normal parathyroid function with parathyroid extract-Collip.

Regardless of the cause of the decreased sugar tolerance induced by insulin in some cases, it is of value to know that this finding is of

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7. van Creveld, S., and van Dam, E.: De invloed van alcoholische pancreasextracten (Insule) op hat gedrag der nieren tegenover glucose, Nederl. tijschr. v. geneesk. **2**:1498, 1923.

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no practical importance. The sugar tolerance returns to normal in a short while. In patients of the series studied it has remained normal two years after the omission of insulin, and there has not been noted sufficient depression of pancreatic function to cause any disturbance in the carbohydrate metabolism when the patients were taking their usual diets.

SUMMARY

This contribution presents a study on the effect of insulin on sugar tolerance in twenty-five thin persons who gained weight by the use of this drug. Tests were made before treatment in nine cases, after one to twelve weeks of continuous administration of insulin in sixteen cases and, finally, from three days to two years after the cessation of administration of insulin in all cases.

Three types of curves for sugar tolerance were obtained. In one, the curves for blood sugar were normal, and the urine remained sugar-free during all the periods of observation. In the second, the curves for blood sugar were normal during the various periods of study, but during the period of administration of insulin glycosuria appeared, usually one or two hours after the ingestion of the dextrose. In the third type, the curves for blood sugar were normal either before or after the use of insulin, but during the period of treatment with insulin there developed a considerable increase in the concentration of the blood sugar in one-half or one hour after the ingestion of dextrose; this was associated with glycosuria, which usually appeared in one or two hours.

The cause of the temporary decrease in tolerance induced by insulin is a matter of speculation. It is suggested that the type of tolerance associated with glycosuria and normal curves for blood sugar is due to a decreased renal threshold and the type associated with glycosuria and hyperglycemia, to either an increased absorption of sugar from the gastro-intestinal tract or a temporrary suppression of pancreatic function.

Regardless of the cause of the glycosuria and hyperglycemia encountered, the finding was of no practical significance, since the sugar tolerance invariably returned to normal shortly after insulin was omitted. Decrease in tolerance to the customary diets employed by these patients while they were taking insulin for the purpose of gaining weight was not observed, even though the diets contained abundant amounts of carbohydrate.

Book Reviews

Tuberculin: Its Vindication by Technique. With Special Reference to Tuberculous Disease of the Eye. By W. Camac Wilkinson, M.D. (London), F.R.C.P., Hon. Director, Tuberculin Clinic, London. Price, 10 shillings, 6 pence. Pp. 93, with 31 illustrations. London: J. & A. Churchill, 1933.

Sixty-eight of the ninety-three pages of this monograph are devoted to a report on the diagnosis and treatment of ocular tuberculosis by tuberculin, and the balance to an impassioned plea for its use in pulmonary tuberculosis. "Nothing can take the place of tuberculin in the early diagnosis of phthisis. It can definitely exclude phthisis as nothing else can, which is a transcendent advantage, but it can also, with other methods, definitely discover that tubercle bacilli are working mischief in the tissues long before any other method can do so. Moreover, as the transcendental remedy for the treatment of early phthisis, it leaves little to be desired. . . ." The author refers to previous reports of his which purport to prove his contention and states that he has a mass of additional evidence but does not present any of it. He pleads for the establishment of about two hundred "Tuberculin Clinics" in London alone, and contends that ambulatory treatment with tuberculin will save taxpayers large sums, and that only patients with the severer types of consumption should be sent to sanatoria. He complains that tuberculin has never been given a fair trial by others, but has been proved by him to be a most potent agent.

The data concerning tuberculin in the diagnosis and treatment of ocular tuberculosis consist of a report on its use in forty-three patients sent to the clinic by oculists in the last five years. In an evaluation of these data one may first question the inclusion of a case of Parinaud's disease and one of "advanced myopia with chorio-retinitis and atrophy," and then comment that in not a single case can the reader venture more than a guess as to what the real condition of the eye was. One is asked to accept the diagnosis without question. For diagnosis the author makes combined intracutaneous and subcutaneous use of the tuberculin (TR.) but does not give details, rules or even the basis for his conclusion that any given case is or is not one of tuberculous disease of the eye except that a temperature and the "track" (local?) reaction were present. Details of treatment, dosage, intervals, what to watch for and other facts are likewise inexcusably meager. In the face of this the author insists that the treatment is often incorrectly given by others. He stresses the value of long-continued treatment—"not for months but for years, even many years."

In one respect, however, the contribution is greatly to be praised, in contrast with various otherwise notable and valuable continental monographs on the use of tuberculin in work on the eye; namely, the author does state in each case the length of time the condition of the eye remained quiescent or "cured" after treatment was completed. Of the forty-three cases, the reviewer would first eliminate eight (the diagnosis was in doubt in three; treatment was still going on in three; in one the patient was still active, and in one the patient had stopped treatment). The thirty-five remaining cases include twenty-six of iridocyclitis (acute and chronic), one of nodular iritis, two of vitreous hemorrhage, two of retinal disease, one of interstitial keratitis and others.

The period of observed quiescence varied from two to forty-five months (with only three observed over three years); it was less than one year in three cases (average, four and one-half months), and in the entire thirty-five cases averaged only sixteen and one-half months.

The reviewre considres this period of observation definitely inadequate. In a follow-up report of fifty cases of iritis, Brown and Irons (The Etiology of Iritis, J. A.

M. A. **81**:1770 [Nov. 24] 1923) set up a period of three years as the shortest period of freedom from recurrence after which one may at all fairly speak of a "cure."

As stated, this record of freedom from occurrence constitutes a very praiseworthy feature of the monograph, inadequate as it is, but there is little else in the work which will stand fair criticism.

L'exploration fonctionnelle de la rate. By E. Benhamou. Price, 50 francs. Pp. 255, with 103 illustrations. Paris: Masson & Cie, 1933.

This book is interesting and to be highly recommended. When one considers that but a few years ago not much was known about the spleen, it is refreshing to discover how great has been the knowledge lately developed regarding the diagnosis and treatment of the various splenic disorders.

Benhamou has attempted to apply to the clinical study of splenic function the physiologic approach to the subject introduced by Barcroft in England, Binet and Pagniez in France and Scheunert in Germany. He then develops his thesis, describing the methods which he employs. He mentions what facts relating to the spleen are to be gleaned by customary physical examination and shows excellent photographic reproductions and charts to demonstrate that most accurate pictures of the organ can be obtained by x-ray either with or without the aid of thorotrast. Of even greater value in determining splenic function, however, is the spleen's response to the subcutaneous administration of epinephrine manifested in the red blood cell count, the white blood cell count, the platelet count, the reticulocytic count and in the character of the circulating leukocytes.

Benhamou believes that spleens which are enlarged from different causes yield varied responses to epinephrine, and that such varied responses afford a means of classifying the underlying pathologic process and suggesting appropriate treatment. In certain instances, for example, splenectomy is indicated, whereas in others this operation is likely to prove fatal so that other forms of treatment are preferable. Study of splenic function helps to separate these two groups.

The book is well printed and bound in paper. A comprehensive bibliography of 303 references completes it. On the whole, the volume deserves favorable comment and should help to stimulate further investigation.

Modern Aspects of Gastro-Enterology. By M. A. Arafa. Price, $8.25. Pp. 374. New York: William Wood & Company, 1933.

In no branch of medical literature is the atavistic tendency more dominant than in textbooks of gastro-enterology. The same exposition of a sharply crystallized body of doctrine appears over and over again modified, perhaps, by the teachings of some physiologist who for the moment is approved by the gastro-enterologic group. There seems to be a curious imperviousness of these books to outside influences; one suspects that there even exists a proscribed list of writings which challenge traditional concepts. It is with interest, therefore, that one approaches Arafa's recent book; one hopes that under the title of "Newer Aspects of Gastro-Enterology" one may find that the house has been cleaned and the cobwebs swept away. Dr. Arafa's work shows all the earmarks of a sincere effort; clearly he has labored industriously in producing this compilation. But the same old outline is followed, and for the most part there is presented only traditional material strongly tinctured by the teachings of the Hurst school.

No two men will agree in all details, and the reviewer finds on nearly every page points with which he would take issue. The statement that "achylia responds to histamine stimulation" in sprue but not in pernicious anemia (p. 68) has not held true in his experience. On page 77 it is said that "evidence is accumulating" that the achlorhydria of later life is due to gastritis; what this evidence is the reviewer does not know. The exposition of the etiology of gastritis—that elusive entity—

goes on with moral fervor if not with medical soundness when one is told that whisky, brandy, liquors and gin are particularly important factors and that gastritis "is not uncommon among young people who frequent cocktail parties." When the author proceeds to say, without any evidence, that "excessive smoking is a common cause (of gastritis), and that tea and coffee may have a similar though more mild, detrimental effects" one's amusement begins to give place to annoyance (p. 77). Nor can the reviewer agree (p. 103) that gastric lavage is a cure for chronic gastritis, or that toxins absorbed from remote "foci of infection" are excreted by the gastric and duodenal mucous membrane, thereby producing peptic ulcer (p. 113). One could continue indefintely.

The book is well written, well illustrated and in every sense useful, and while not the reviewer's ideal of what can be done in this domain, it has fewer positive demerits than other textbooks of gastro-enterology with which he is familiar.

History of Urology. Prepared under the auspices of the American Urological Association. Editorial Committee, Edgar G. Ballenger, William A. Frontz, Homer G. Hamer and Bransford Lewis, Chairman. Two volumes. Price, $8. Pp. 746, with illustrations. Baltimore: Williams & Wilkins Company, 1933.

These two volumes combine to make an interesting book. It was written by thirty-two well known contributors, and deals primarily with the history of urology in this country. As Dr. Wishard suggests in the preface, the specialty is a youthful one. It began in 1874 with the publication of Van Buren and Keyes's "Genito-Urinary and Venereal Diseases," soon gathered momentum and has made amazing strides since 1900. Any one who enjoys reading about medical personalities will like the first eight chapters of this history. These give short accounts of the pioneer urologists in various parts of the country, showing how urology came to be recognized as a specialty through the work of various leaders of medical and surgical thought all over the United States.

The remainder of volume 1 and all of volume 2 deal more directly with the development of present knowledge regarding various phases of the specialty. Anatomy, physiology and bacteriology, as well as improving technics, instruments, diagnostic measures, roentgenology and methods of anesthesia and therapy, are discussed. Each of these chapters is written in an orthodox textbook style and has references appended so that all the pertinent literature is made easily available.

The editorial board has worked carefully. There is a certain amount of unevenness in the manner in which various chapters have bene written, and occasionally names are spelled incorrectly. Considering the number of contributors, however, and the size of the two volumes, there is little to be criticized. The printing is good, and the illustrations are sufficiently clear and interesting. On the whole, this "History of Urology" lends dignity and completeness to any medical library.

Peptic Ulcer. By Jacob Buckstein. Second edition. Price, $12. Pp. 417, with 334 roentgenograms and 77 illustrations. New York: Paul B. Hoeber, Inc., 1933.

The second edition of this monographic atlas has been considerably enlarged by the addition of 121 illustrations and the incorporation of the latest literature on the subject. The result is a splendid book replete with illustrations which will be of great value to the roentgenologist who has a relatively slight opportunity of observing many cases of peptic ulcer. This book and the other monographs in the series have been prepared in order to supply a series of master roentgenograms for study and for comparison. Just how the atlas would fit into the library of the internist is a rather difficult question to answer. Of course, it would be of considerable value to the roentgenologist who makes roentgen diagnoses at relatively frequent intervals, but whether or not the high initial cost of the book would repay the rather infrequent reference to it by the practitioner when questionable films of the upper alimentary tract come up for interpretation

would be a difficult matter to judge. It would seem that the atlas would be employed almost entirely by the roentgenologist and would be of decidedly limited value to the internist.

The atlas is beautifully illustrated. The format is what one has come to expect of Hoeber's books.

La angina de pecho. By Dr. Gregorio N. Martinez. Pp. 278. Buenos Aires: Humberto Andreetta, 1933.

This is an excellent monograph on angina pectoris based on the author's experience and on an extensive review of the literature. The bibliography contains 652 titles. The book is well illustrated not only with electrocardiograms, but with attractive colored illustrations. Particularly interesting are the ones showing diagrammatically the various operations that have been performed with the hope of relieving the pain of angina. The author inclines to the view that the ideas of Danielopolu are the nearest correct. He realizes that many of the attempts at operative relief have failed, but he believes that enough of them have been successful to warrant further attempts along this line.

As one would expect, there is not much new in regard to either pathology or treatment, but to any student of the subject able to read Spanish this book can serve as a splendid introduction to the subject of angina. The author is particularly to be congratulated on having been able to cover the literature so well while working in a country far removed from the larger medical libraries.

Arteriosclerosis. Edited by Dr. E. J. Cowdry. Price, $5. Pp. 617, with 88 illustrations. New York: The Macmillan Company, 1933.

This volume is a publication of the Josiah Macy, Jr., Foundation and aspires to bring together current knowledge and opinion regarding the changes in the blood vessels generally termed arteriosclerosis. It is a compilation of ideas from various sources: The authors are drawn from Europe and England, as well as from different sections of this country.

The subject matter is well arranged, beginning with a historical review by Dr. Esmond R. Long of Philadelphia of how present knowledge regarding arteriosclerosis has developed, and ending with a critical review of the contents of the book by Dr. Alfred E. Cohn of New York. Throughout, one finds chapters on the different phases of vascular disease written from various points of view by thoroughly competent authorities.

On the whole, the book is excellent for reference. It is well printed and illustrated; each chapter is clearly written, and the literature is covered adequately. All medical libraries will wish to own a copy.

Le sinus carotidien et la zone homologue cardio-aortique. By C. Heymans, J. J. Bouckaert and P. Regniers. Price, 55 francs. Pp. 334. Paris: Gaston Doin & Cie, 1933.

The name of Heymans has been prominently associated with work on the problems of the carotid sinus, and the present volume of which Heymans the younger is chief author is dedicated to his father. While (and properly) a great deal of emphasis is placed on the work of the Belgian group, the subject is treated in systematic form, and the literature in general is well covered. Each topic, such as the relation of the carotid sinus to respiration or to blood pressure, receives detailed and critical consideration. The experimental support for any claims is well presented, and clinical implications are exposed.

The physiologist working in this special domain will doubtless take issue with certain points, but in any event the monograph represents a monumental collection of material. The style is elegant, the format pleasing, and to the worker who wishes quickly to inform himself on the status of the subject the work should prove invaluable.

Food and the Principles of Dietetics. By Robert Hutchinson and V. H. Mottram. Seventh edition. Price, $7.25. Pp. 630. New York: William Wood & Company, 1933.

Many books are available on practical dietetics as well as on the composition of foods. Few, however, combine a thorough discussion of feeding from both of these angles. In the present instance a happy combination has been achieved, the result of which should be of great help to the practicing physician; that such is actually the case is witnessed by the fact that this is the seventh edition of Hutchinson and Mottram's treatise, the first having appeared in 1900. The reviewer is especially impressed by the scholarly fashion in which the nature of foods, their individual composition, their digestibility and their fate in the body are discussed; with bread, for example, one is told about wheat, the milling process and the making of flour, and is enlightened as to the baking of bread, the composition of the final loaf, its nutritive value and even its economic status. The sections on diet in special diseases are terse but adequate. The bibliography is well selected, and the index is complete.

Fortschritte der Serologie. By Hans Schmidt, M.D., Professor of Hygiene, Institute for Experimental Therapy, Marburg. Paper. Price, 12 marks. Pp. 196, with 20 figures. Dresden: Theodor Steinkopff, 1933.

This book is the thirtieth part of a series of short German monographs which have been appearing from time to time since 1921, designed to summarize the progress of investigation in different paths of science. This particular publication deals, as its title suggests, with recent progress in serologic tests.

The book is well printed and clearly written. The subject matter covers such topics as the formation of antigen; the phenomena of agglutination, precipitation and hemolysis; complement fixation; phagocytosis; bacteriolysis; the formation of toxin and antitoxin, and lipoids in serologic reactions. The bibliography is adequate, with abundant references to constructive work which has been completed in various American, English, French and German laboratories. A complete table of contents is appended. On the whole, the book is useful for reference, and will make an acceptable addition to many medical libraries.

Les fonctions gastro-duodénales. By J. Dimitresco-Popovici. Paper. Price, 28 francs. Pp. 250. Paris: Masson & Cie, 1932.

This book gives a rapid and necessarily incomplete summary of physiologic and clinical researches on the stomach and duodenum, including some of the author's own work. The book should prove to be stimulating to the American reader, who will find no mention of much that has excited attention in this country, but instead will find occasional things which have escaped his notice in the European literature. One must regret the unusual number of inaccuracies and omissions in the bibliography and the absence of an index.

The Therapeutic Agents of the Quinoline Group. By W. F. von Oettingen, M.D., Ph.D. American Chemical Society Monographs. Price, $6. New York: The Chemical Catalog Company, Inc., 1933.

This book is really a small encyclopedia on the subject. About 500 derivatives of the quinoline group are discussed from every possible angle: chemical, pharmacologic, physiologic, toxicologic and therapeutic. Little more can be said in review; the monograph seems to cover the subject to date in a definitive manner. The bibliography includes about 1,000 titles.

La función hemo-respiratoria en los "Cardiacos Negro de Ayerza." By Isaac Berconsky. Buenos Aires: Biblioteca de la Facultad de Ciencias Medicas, 1933.

This rather brief monograph on Ayerza's disease represents almost entirely a more or less philosophic discussion of the various explanations that have been brought forth to explain the cyanosis that occurs in the disease. It is an excellent review of the literature, without presenting any new experimental evidence as to the mechanism of the production of the disease.

News and Notes

GERMAN SOCIETY FOR CIRCULATORY RESEARCH

The seventh convention of the German Society for Circulatory Research (Deutsche Gesellschaft für Kreislaufforschung) will be held at Bad Kissingen on April 16 and 17, 1934. The subjects to be discussed are thrombosis and embolism.

Applications for participation will be accepted until March 1 by Prof. E. Koch, Bad Nauheim.

A detailed program will be mailed to those who register.

PROF. DR. J. NÖRR, *Chairman*,
München, Veterinärstr. 6

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